Chiral Heterocyclic Ligands

A thesis submitted in partial fulfilment of

the requirements for the Degree of

Doctor of Philosophy in Chemistry

at the

University of Canterbury

by

William Lewis

University of Canterbury

Christchurch

New Zealand

2007

Acknowledgements

First thanks must go to my supervisor, Professor Peter J. Steel, who provided a fascinating project to work on. His guidance and patience has been a constant throughout the project. I also have to thank all the past and present members of the Steel group, as well as other occupants of room 658. My fellow PhD students Chris F, Chris S, Jennifer, Justine, Jenny have been a pleasure to work with, while the various Postdoctoral Fellows, Dave, Jon, Matt and Chris R have offered excellent advice and suggestions.

I would like to thank the Chemistry Department as a whole. The academic staff have all been helpful at one time or another, and are always happy to answer questions or point a student in the right direction. The technical staff are a highly skilled group, and many thanks must go to them for keeping the department and its various pieces of equipment running.

Finally I have to thank my family, particularly my parents, Zelda and Tony, and my brother Michael, for their continued love, support and encouragement.

Table of Contents

Abstract

This thesis describes the preparation and characterisation of a number of homochiral coordination and metallosupramolecular assemblies. These species were formed from the reaction of chiral pyridine and quinoline containing ligands and metal ions. The combination of traditional coordination chemistry and supramolecular interactions led to a range of polymeric and network structures being formed.

The ligands used in this thesis can be divided into two broad categories: alkaloids and ligands derived from them, and amino acid-based ligands. In the first category three new ligands were synthesized, and a variety of routes towards alkaloid-based homochiral ligands were investigated. The second category focused on three ligand motifs, and resulted in the preparation of 16 ligands. These two categories of ligands were reacted with a range of metal salts to investigate their coordination and supramolecular chemistry.

The structure of twenty complexes was determined by single crystal X-ray crystallography. The complexes had a range of structures, with discrete and polymeric species being formed. Hydrogen bonding was an important feature in the supramolecular chemistry of the complexes, playing a different role in different series of complexes.

Two chiral coordination polymers and one chiral coordination network were synthesized. All three of these structures possessed directionality to some degree: in the coordination network and one of the polymers the directionality is counterbalanced by the opposite directionality being present in the crystal, while the second coordination polymer is generated by the screw axis present and has a high degree of overall directionality.

Introduction

1.1 Background

In transition metal coordination chemistry one of the most important classes of ligands is the nitrogen heterocycles.[1, 2] The most widely studied of these are pyridine, 2,2'-bipyridine and 2,2':6',2"-terpyridine (see Figure 1.1). Due to interactions between the π* antibonding orbitals of the ligand and the d-orbitals of a metal ion, strong coordinate bonds are formed, resulting in stable complexes. Other related ligands that have been extensively employed in coordination chemistry are the five membered nitrogen heterocycles pyrazole and imidazole (see Figure 1.1).

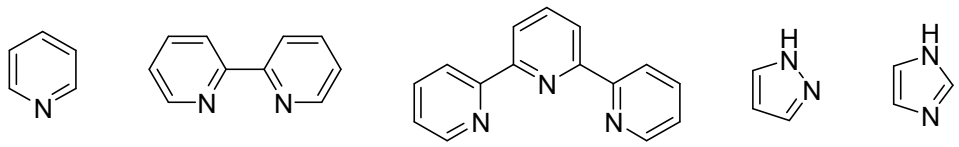


Figure 1.1: From left to right, pyridine, 2,2'-bipyridine, 2,2':6',2"-terpyridine, pyrazole and imidazole.

The incorporation of two or more of these donors into a single molecule can result in species which can bridge between two metal centres, chelate to a single metal centre, or a combination of both these motifs. Chelation to a metal centre increases the stability of the complex, and so is desirable for inclusion into the design of ligands. The bridging of metal centres by a ligand can result in communication between the metal centres, as well as resulting in higher order molecular architectures. These include discrete species, such as molecular squares, cubes and cages, and polymeric species such as chains, ladders, helicates and metal-organic frameworks.

1.2 Chirality

Chirality is an extremely common feature in molecules, and can be defined as a molecule which is not superimposable on its mirror image. The most common and well-studied type of chirality is that of the tetrahedral carbon atom, which has

been recognized since 1874.[3] Other types of chirality in organic chemistry include planar chirality, atropisomerism and molecules with stereochemical axes. These molecules have non-superimposable mirror images that are not based on a tetrahedral carbon atom with four different substituents.

Chirality in coordination chemistry is a relatively more complex subject. With a wide range of coordination numbers and coordination geometries at the chiral centre (often, but not always the metal centre), there is a greater range of types of chirality in coordination compounds.

There are two extremes in synthesizing a chiral complex: to attach a chiral ligand to an achiral complex and to synthesize a metal centre that is chiral. These can be viewed as two extremes of a continuum, with cases occurring in which both of these occur, as well as many in which this type of description would be an oversimplification.

Two of the best studied in inorganic systems are the *Δ* and *Λ*- forms of tris-bidentate substituted octahedral centres, and the *P*- and *M*- forms of helicates. In any typical synthesis of coordination compounds it is possible that all the stereoisomers can form, as with organic syntheses, although external factors can more significantly affect these syntheses to favour one product over another.

When a metal complex is synthesized with an aim to create a chiral metal centre there are two possible methods. These mirror to some extent the synthesis of chiral organic molecules. The first is synthesis of a single stereoisomer, which would have to involve some sort of stereoselective synthesis. Potential methods for this type of synthesis are the use of chiral anions during the synthesis, the use of a chiral auxiliary to direct the synthesis, or use of a chiral ligand (which would have to be synthesized itself, see below). The other method is to synthesize multiple stereoisomers and then separate them. One example of a method of separation is fractional crystallization with a chiral anion. The aforementioned separation is a specific example of the method generally used to separate these types of complexes: these separations involve the temporary or permanent formation of diastereoisomers; these have different physical

properties and so may be separated by a number of methods. One example is the work of Fletcher and Keene,[4] which involved the separation of diastereomeric diruthenium complexes by chromatography. They demonstrated that intelligent selection of the anion used for elution would result in separation of the diastereoisomers.

The other extreme in the synthesis of chiral complexes is to attach a chiral ligand to an achiral metal centre, resulting in a chiral complex. Although this method seems simpler than the previous method, it moves the origin of chirality further up the synthetic chain. The synthesis of a chiral ligand then becomes an important step towards the synthesis of a chiral coordination compound.

As with the synthesis of a chiral metal centre, there are three methods of obtaining a chiral ligand. The first is the synthesis of a chiral centre, with a stereoselective synthesis resulting in a single stereoisomer. The second method is synthesis of two stereoisomers, followed by separation. The final method is to start with a single stereoisomer and use that in the synthesis of the chiral ligand. This is the approach used in this thesis.

Chiral ligands play an important role in coordination chemistry, and have been used extensively in catalysis.[5] A wide range of phosphorus containing ligands is known, and have found widespread use in enantioselective catalytic processes.[6] Nitrogen containing heterocycles have not been utilized as extensively, although a number are known.[7]

Four common sources of chiral materials in nature, which are part of the chiral pool, are carbohydrates, amino acids, terpenes and alkaloids. Each of these classes has been incorporated into chiral heterocyclic ligands for use in coordination chemistry. Carbohydrates, a common example of which is glucose (see Figure 1.2), have been the least utilized in this context. Terpenes are the most commonly used chiral starting material, due to their ease of incorporation in synthesis. Examples such as the pinenes[5] and camphor[8] (see Figure 1.2) have been widely incorporated into heterocyclic ligands.

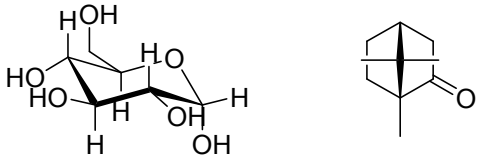


Figure 1.2: α-(*D*)-Glucose, a carbohydrate, and (1*R*)-(+)-camphor, a monoterpene.

Amino acids have mainly been used in the synthesis of amino alcohols, for incorporation into chelating oxazolines[9, 10] (see Figure 1.3) and related ligands.

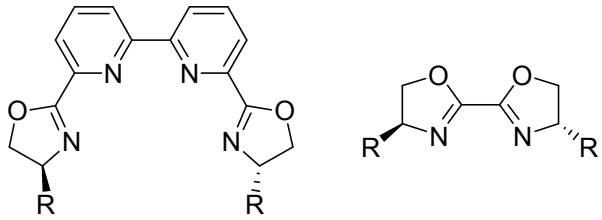


Figure 1.3: Two examples of chelating oxazolines synthesized from amino acids.

Alkaloids are a class of compounds isolated from plants, in which their function is largely unknown, and thousands have been structurally characterized. Alkaloids have found little use in coordination chemistry, or indeed in organic chemistry. The notable exception to this is the ligands used in the asymmetric Sharpless dihydroxylation,[11] which are derived from the cinchona alkaloids.

1.3 Supramolecular Chemistry

Supramolecular chemistry[12, 13] is defined as “chemistry beyond the molecule, bearing on the organized entities of higher complexity that results from the association of two or more species held together by intermolecular forces.”[13, 14] Traditional chemistry relies on covalent bonds between atoms to hold molecules together, and, as such, atoms are the building blocks of molecules. One of the key concepts of supramolecular chemistry is that the molecules themselves are the building blocks of larger aggregates.

In traditional chemistry covalent bonds hold the atoms together to form molecules, and these bonds typically have strengths in the region of 350 kJ

mol^{-1}. In supramolecular chemistry a range of weaker interactions is considered; examples include hydrogen bonding, ion-dipole, dipole-dipole and π-π Stacking. Hydrogens bonds are relatively common in chemistry, and occur when a hydrogen atom is bonded to an electronegative or electron deficient atom and is in close proximity to an acceptor atom which is electron rich. Hydrogen bonds are defined as the sharing of the hydrogen nucleus, or proton, between the donor and acceptor. Hydrogen bonds typically have strengths in the 5-50 kJ mol^{-1} range,[15] which is significantly less than a covalent bond. π-π stacking is another common interaction considered in supramolecular chemistry, and a number of different types exist.[16] The strength of this type of interaction has a typical range of 0-20 kJ mol^{-1}.

"Metallosupramolecular chemistry" was a term first introduced by Constable,[17] and refers to aggregates formed by the combination of organic molecules and metal ions. Similar to supramolecular chemistry (of which it is a subset), this area also considers interactions other than the covalent bond. Combinations of weak interactions lead to complex structures, and the introduction of metal atoms has led to a range of interesting new topologies, such as macrocyclic polyhedra,[18] helicates,[19] and numerous types of coordination polymers and networks.[20, 21]

A key concept in supramolecular chemistry is self assembly. This refers to the self-organisation of materials resulting in a single supramolecular species. The choice of starting materials and their ratios have a significant effect on the products. The use of weak interactions, rather than covalent bonds, allows continual breaking and reforming to occur, resulting in thermodynamic control. The outcome of self-assembly is that the thermodynamically most stable product will eventually be formed. An alternative description of this process is "error checking".

In metallosupramolecular chemistry the choice of building blocks is an important feature of the process. Transition metals have a wide range of coordination numbers and geometries, and with extension to the lanthanides, this can increase even more. Additional properties of the metal ions can be used to obtain different results. The lability of the metal ion chosen can be used to tune

the self-assembly process, while luminescence, and other spectroscopic and electronic properties can be incorporated by choice of an appropriate metal centre.

The other building blocks in metallosupramolecular chemistry are the organic ligands. There is a wide range of different potential geometries available, and imaginative synthesis can provide almost any desired shape.

1.4 Applications

Coordination complexes, supramolecular and metallosupramolecular aggregates are investigated in a wide range of areas. Beyond general coordination chemistry[1] they are of interest in areas such as new materials research, host-guest chemistry and solid state reactions.

Chiral complexes are of particular interest in materials science. For example, the use of chiral coordination polymers is important in the area of non linear optics.[22]

1.5 Thesis Coverage

Nicotine and the cinchona alkaloids are readily available, homochiral, aromatic heterocycles. They make an ideal starting point for the investigation of chiral coordination and metallosupramolecular species. In Chapter 2 the coordination and metallosupramolecular chemistry of the unmodified alkaloids is explored. In Chapter 3 the modification of nicotine and the cinchona alkaloids towards the synthesis of new homochiral aromatic heterocycles is investigated. Chapter 4 extends from alkaloids to incorporating amino acids into chiral ligands. Chapter 5 reports the coordination and metallosupramolecular chemistry of the ligands synthesized in the previous chapter.

Metal Complexes of Alkaloids

2.1 Introduction

In this chapter the coordination and metallosupramolecular chemistry of two members of the alkaloid family of compounds, namely nicotine and quinine, are described. As outlined in Chapter 1, these compounds are homochiral ligands, consisting of only one enantiomer, and hence can be expected to result in pure chiral complexes.

2.1.1 Nicotine

Nicotine (see Figure 2.1) consists of a pyridine ring, substituted at the 3-position with an N-methyl-pyrrolidine ring. Nicotine is extracted from the *Nicotiana tabacum* plant, although it is found in smaller amounts amongst other plants of the *Solanaceae* family. Previous work on the coordination chemistry of nicotine has been limited to a few studies, and only a limited number of crystal structures of complexes have been described.

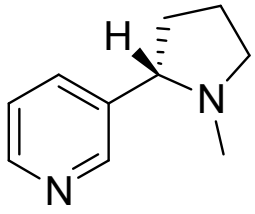


Figure 2.1: Nicotine

Original work on the coordination chemistry of nicotine was carried out by Smith,[23] who investigated the synthesis of nicotine "double salts" of various metal salts. Some of these complexes have been synthesized and their three-dimensional structures explored via X-ray crystallography; this is described in Section 2.2.1 of this chapter.

Prior to commencement of this work, only three crystal structures of metal complexes of nicotine had been reported, although a number of iodide salts of nicotine had also been determined by X-ray crystallography.[24] The first crystal

structure of a metal complex of nicotine was determined by Udupa and Krebs,[25] and describes a structure in which nicotine acts as a bridging ligand between tetrahedral Hg(II) centres, forming a one-dimensional coordination polymer. Subsequently an investigation by Haendler,[26] detailed the crystal structure of a complex in which four nicotine molecules are coordinated to an interesting Cu_4Cl_6O core (see Figure 2.2). In this structure nicotine acts a monodentate ligand, coordinated via the pyridine nitrogen. The most recent of these three crystal structures was an investigation by Peulecke and co-workers.[27] In this study nicotine acts as a monodentate ligand, coordinated via the pyridine nitrogen to a zirconium complex.

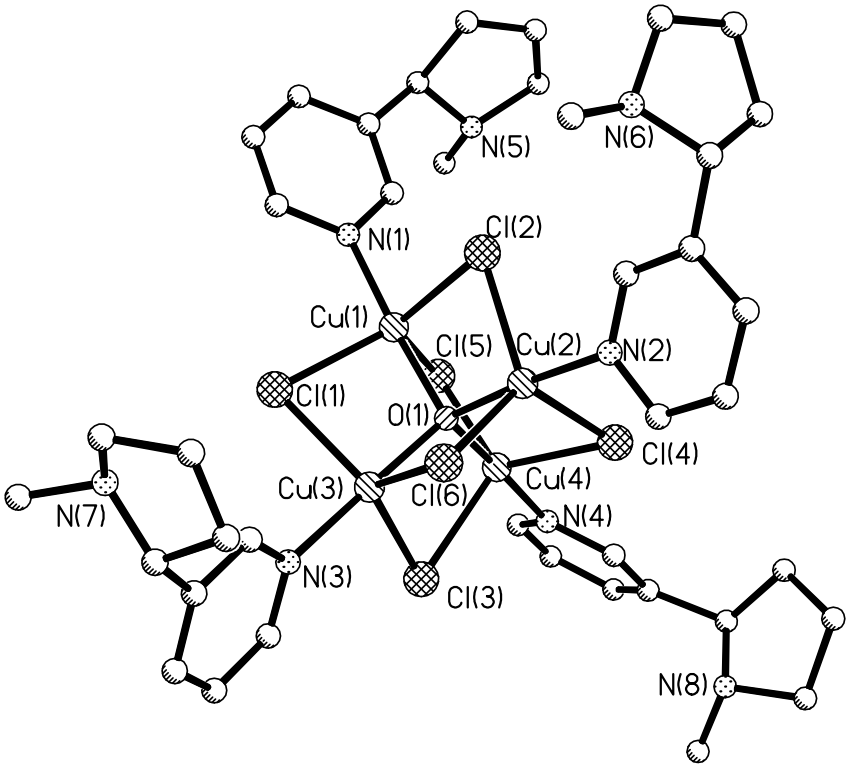


Figure 2.2: A perspective view of the crystal structure determined by Haendler, showing the Cu_4Cl_6O core and the pendant nicotine molecules. Hydrogen atoms are omitted for clarity.

After this project had commenced, four more X-ray crystal structures were published which use nicotine as a ligand. A paper by Guan and Fischer[28] reported three related complexes, each consisting of a lanthanide metal coordinated to three indenyl ligands and a single, pyridine linked, nicotine

molecule. More recently, Meyer and co-workers[29] reported a silver(I) complex identical to complex **9** reported in this chapter (see Section 2.2.2).

Comparison of all previous X-ray crystal structures reveals that only two of the possible three bonding modes of nicotine (see Figure 2.3) have been observed; coordination of the pyridine nitrogen, and coordination of both the pyridine and pyrrolidine nitrogens, where the nicotine molecule acts as a bridging ligand.

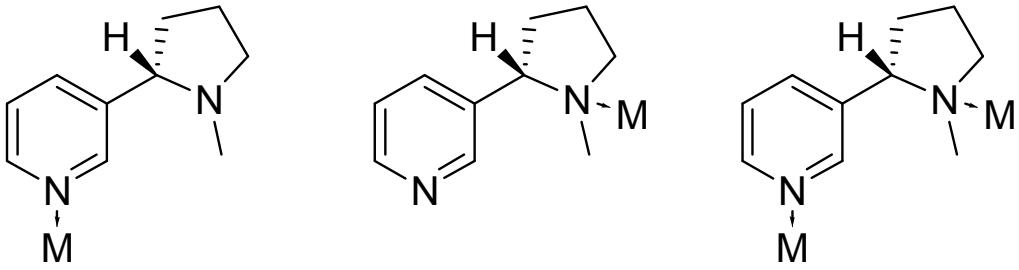


Figure 2.3: The three possible coordination modes of the nicotine molecule. From left to right: monodentate coordination via the pyridine nitrogen, monodentate coordination via the pyrrolidine nitrogen, bridging bidentate coordination via both nitrogens.

2.1.2 Quinine and the Cinchona Alkaloids

Quinine is the best-known member of the cinchona family of alkaloids. These alkaloids all have the same basic form (see Figure 2.4), with two different subsets related by the change from a methoxy-substituent to a hydrogen atom. There are five different stereocentres within the quinine molecule, however only 2 of these vary between different members of the family. Having only two variable stereocentres (at C9 and C10 – see Figure 2.4) means that there are four different diastereoisomers. As the other stereocentres do not vary, there are no true pairs of enantiomers amongst the family; however, due to chemical similarity of these different diastereoisomers, they have sometimes been dubbed “pseudo-enantiomers”. An example of this is quinine and quinidine.

Quinine (and the related cinchona alkaloids) possesses four possible coordination sites. The most obvious is the quinoline nitrogen, and this has been

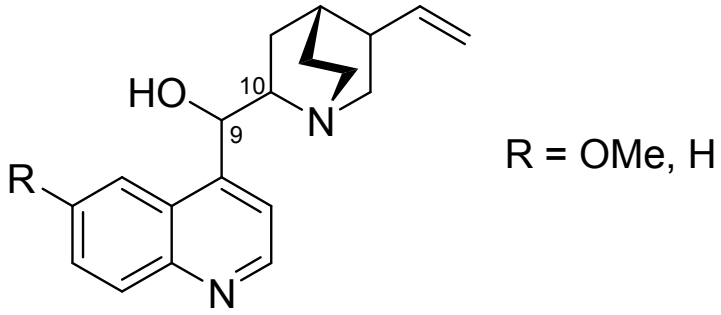


Figure 2.4: A schematic representation of the cinchona alkaloids.

reported in the work of Oleksyn and co-workers,[30] and Beck,[31] and the work of Xue and co-workers.[32, 33] The amine nitrogen is the second obvious donor site; this site has not been observed to coordinate in any complexes with quinine as a monodentate donor. The third site is the alcohol oxygen, and again, this site has not been observed in any complexes with quinine as a monodentate donor. However these two donor sites can coordinate in a cooperative fashion, with quinine acting as a bidentate chelating ligand. This coordination mode has been observed in the work of Hubel, Polborn and Beck,[31] as well as Missling and co-workers.[34] The final coordination mode is via the vinyl group; this coordination mode has been observed in the work of Hubel, Polborn and Beck,[31] and by Xie and co-workers.[32] It should be noted that the work of Xie and co-workers[32] involves the synthesis of coordination networks formed by copper(I)-halide clusters and bridging cinchona alkaloids, with coordination to both quinoline nitrogen and the alkene group. The work of Hubel, Polborn and Beck[31] involves discrete complexes utilising each of the three coordination modes above, as well as a discrete complex that involves coordination to both the quinoline nitrogen and the chelating bidentate donor set.

2.2 Complexes of Nicotine

2.2.1 Complexes of Nicotine: $M(SCN)_4(Nicotine.H)_2$ Series

Initial investigation of transition metal complexes of nicotine involved the repetition of syntheses from the work of Smith.[23] This paper detailed the synthesis and elemental analysis of a number of nicotine-transition metal complexes, although no further structural elucidation was attempted.

Synthesis of the Complexes

All the complexes were prepared by reacting an aqueous solution of an appropriate metal salt and ammonium thiocyanate with an ethanolic solution of nicotine. Slow evaporation of the solution generally furnished crystals suitable for X-ray crystallography. Cobalt(II) (**1**), nickel(II) (**2**), copper(II) (**3**), and cadmium(II) (**4**) complexes were all synthesized in this manner, with yields of 88%, 98%, 29% and 75%, respectively.

Synthesis of an iron(II) complex (**5**) required the use of deoxygenated solvents under an inert atmosphere (N_2), and resulted in a small number of low quality crystals, as well as a large amount of non-crystalline by-products. Although the crystals appeared of high quality, and even gave apparently high quality data, a solution to the crystal structure could not be found. The crystal system and space group were readily identified, and were in close agreement with other complexes in this series (see Table 2.1). However the lack of a structural solution makes the exact nature of this complex uncertain. The most that can be said is that this complex resembles others in the series.

Synthesis of a manganese(II) complex (**6**) involved the same deoxygenated solvent/inert atmosphere conditions as that of the iron complex, as well as the use of freshly recrystallized manganese(II) acetate. This complex crystallized as

a large number of poor quality crystals, which were relatively unstable to the presence of oxygen. The low crystal quality meant that although the crystal structure could be solved, with the same motif observed as in the previous structures, it could not be refined satisfactorily. The instability of the product to oxygen precluded any further analysis, as the submitted product was invariably contaminated with manganese(IV) oxide.

The copper(II) complex (**3**) could also be synthesized in an alternative manner to that detailed above. An attempt was made to synthesize a copper(I)-nicotine-thiocyanate complex by combining a solution of tetrakis(acetonitrile)copper(I) tetrafluoroborate in acetonitrile with a solution of nicotine in 40% aqueous calcium thiocyanate solution. Slow evaporation of the solution provided crystals suitable for X-ray crystallography, which proved identical to those provided by the earlier synthesis.

Initial synthesis of the nickel(II) complex (**2**) was also different to that detailed above, and resulted in more than one crystalline product being formed. Reaction of hexa(aqua)nickel(II) perchlorate dissolved in water with a solution of nicotine in ethanol was followed by addition of a solution of sodium thiocyanate in water. Upon addition of the final solution a pale blue precipitate formed. After further standing for ~3 days two different crystalline products had formed, pale blue crystals (**2**) (which ultimately were identical to those synthesized using the method detailed above) and purple crystals (**7**- see Section 2.2.3). The purple and pale blue crystals were separated by manual sorting under a microscope.

Structure of 1

Complex **1** crystallizes in the monoclinic space group C2, as a 2:1 ligand:metal complex. Hydrogen bonding between adjacent complexes forms a two-dimensional network in the *xy* plane. The asymmetric unit consists of a cobalt centre on the 2-fold axis, coordinated to a nicotine molecule via the pyridine nitrogen, as well as two N-bound thiocyanates. Generation of the symmetry equivalent thiocyanates and nicotine reveal the octahedral geometry of the

cobalt centre, with the nicotine molecules having a *trans* relationship (see Figure 2.5). The charge balance of the complex is accounted for by protonation of the

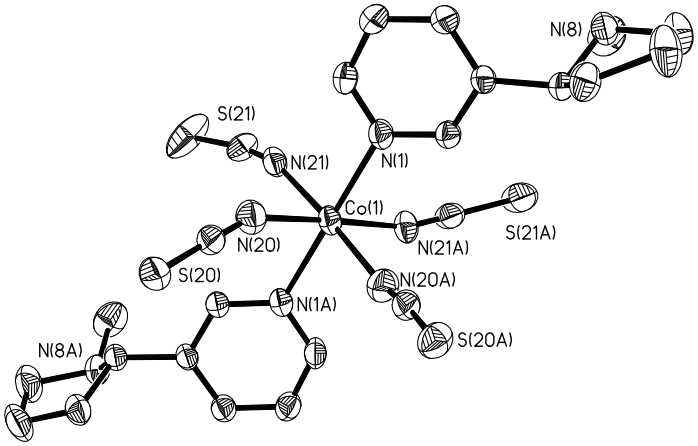


Figure 2.5: A perspective view of 1, with symmetry equivalent nicotine and thiocyanates denoted by the suffix A. Hydrogen atoms and the minor component of the disordered thiocyanate sulfur atoms are omitted for clarity. Selected bond length (Å) and angle (°): Co(1)-N(1) 2.180(2), Co(1)-N(20) 2.134(2), Co(1)-N(21) 2.088(2), N(1)-Co(1)-N(1A) 179.59(11), N(1)-Co(1)-N(20) 91.11(8), N(1)-Co(1)-N(20A) 88.59(8), N(1)-Co(1)-N(21) 92.42(7), N(1)-Co(1)-N(21A) 87.86(7), N(20)-Co(1)-N(20A) 85.33(11), N(20)-Co(1)-N(21) 89.84(8), N(20)-Co(1)-N(21A) 175.09(8), N(21)-Co(1)-N(21A) 95.00(11).

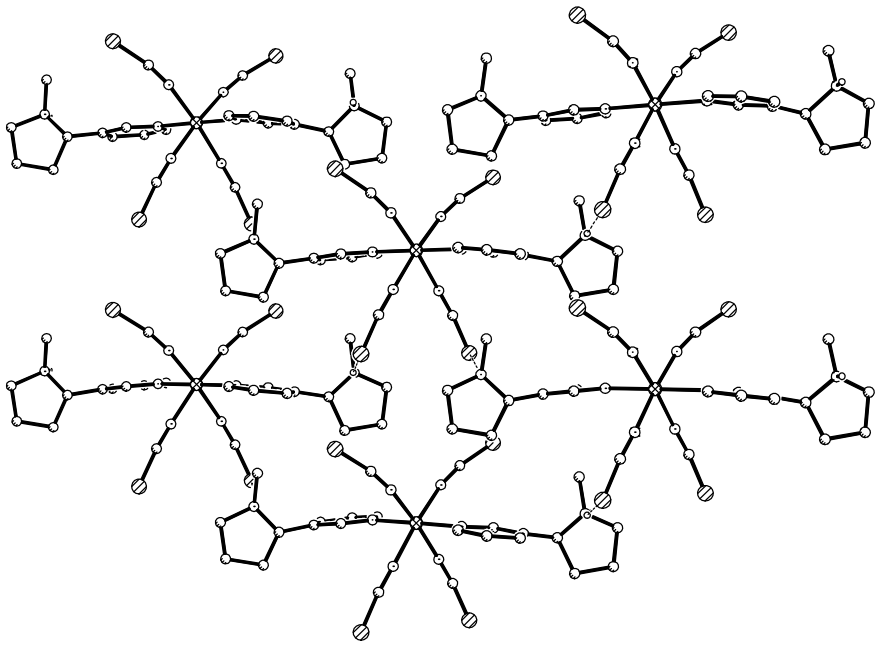


Figure 2.6: A perspective view of the (4,4) hydrogen bonding network looking down the *z*-axis. Hydrogen atoms and minor components of the disordered sulfur atoms are omitted for clarity.

amine nitrogen of the nicotine molecule. This proton was located from the electron density difference map, and then placed in a calculated position. Both the terminal sulfur atoms of the thiocyanates are disordered over two positions. Two of the four thiocyanates (symmetry equivalent to each other) are hydrogen bonded to the protonated amines of an adjacent cobalt unit, to form a two-dimensional network. This (4,4) network extends in the *xy*-plane (see Figure 2.6).

Structure of 2

The structure of **2** (see Figure 2.7) is isostructural with that of **1**; it crystallizes in the monoclinic space group C2, as a 2:1 ligand:metal complex. It possesses the same intra- and inter-molecular structural features, including an identical hydrogen bonding network.

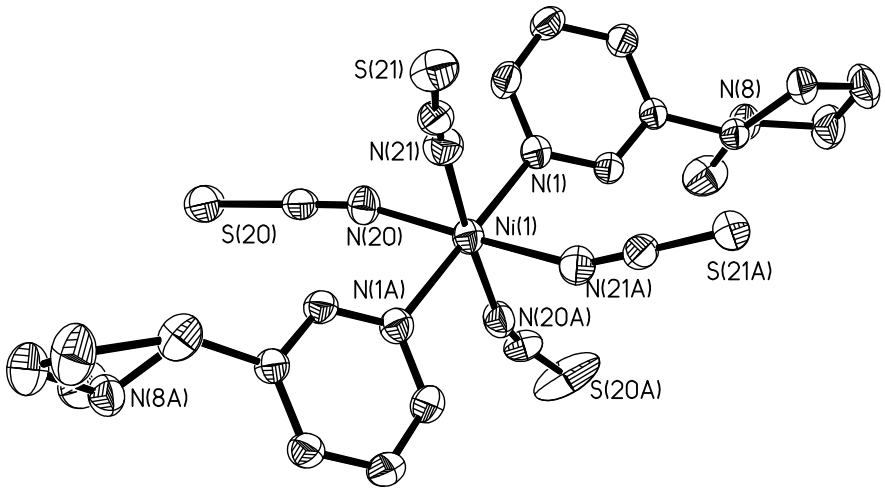


Figure 2.7: A perspective view of complex 2. Hydrogen atoms and the minor component of the disordered thiocyanate sulphurs are omitted for clarity. Selected bond lengths (Å) and angles (°): Ni(1)-N(1) 2.125(3), Ni(1)-N(20) 2.066(3), Ni(1)-N(21) 2.097(3), N(1)-Ni(1)-N(1A) 179.72(18), N(1)- Ni (1)-N(20) 92.28(13), N(1)-Ni(1)-N(20A) 87.91(13), N(1)-Ni(1)-N(21) 91.03(13), N(1)-Ni(1)-N(21A) 88.76(13), N(20)-Ni(1)-N(20A) 93.40(19), N(20)-Ni(1)-N(21) 90.43(14), N(20)-Ni(1)-N(21A) 176.06(14), N(21)-Ni(1)-N(21A) 85.7(2).

Structure of 3

Complex **3** crystallizes in the monoclinic space group $P2_1$, as a 2:1 ligand:metal complex. Hydrogen bonding between adjacent complexes forms a one-dimensional polymer along the *y*-axis. As opposed to the previous two structures, **3** crystallizes with the entire copper unit in the asymmetric unit. The copper centre has a square pyramidal geometry, with three nitrogen bound thiocyanates (one in the apical position), and two pyridine bound nicotines, *trans* to each other. Both nicotine molecules are protonated at the amine nitrogen, and the charge balance is accounted for by a non-coordinated thiocyanate anion, which is hydrogen bonded to one of the amine protons via the nitrogen terminus (see Figure 2.8). The bond distances between the copper and the ligands are typical of such complexes, ranging from 1.980(3) to 2.044(3) Å for the basal ligands, and 2.223(3) Å for the apical thiocyanate, showing the expected Jahn-

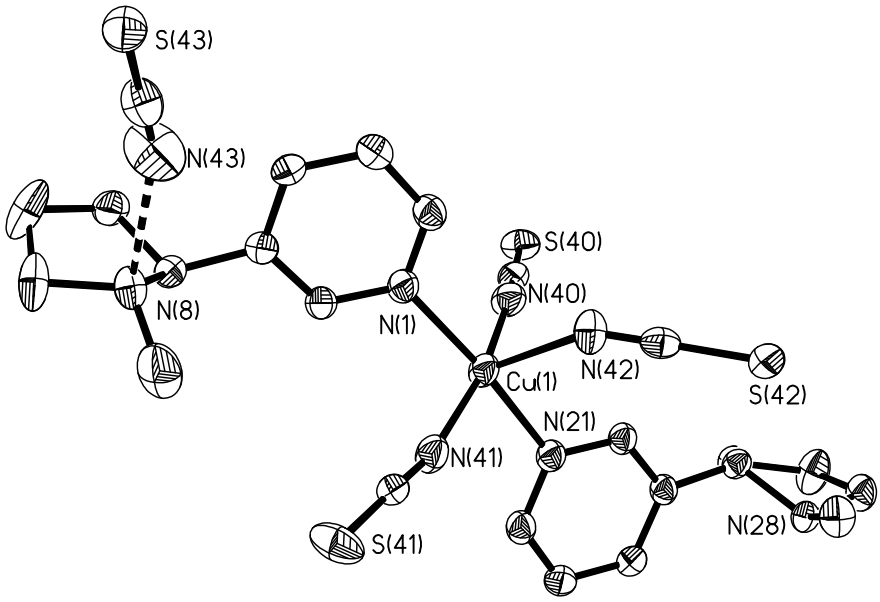


Figure 2.8: The asymmetric unit of complex 3. Hydrogen atoms and the minor component of the disordered thiocyanate sulfur atom are omitted for clarity. The hydrogen bond between N(8) and N(43) is shown as a dashed line. Selected bond lengths (Å) and angles (°): Cu(1)-N1 2.044(3), Cu(1)-N(21) 2.057(2), Cu(1)-N(40) 2.001(3), Cu(1)-N(41) 1.980(3), Cu(1)-N(42) 2.223(3), N(1)-Cu(1)-N(21) 172.99(12), N(1)-Cu(1)-N(40) 90.82(12), N(1)-Cu(1)-N(41) 87.91(11), N(21)-Cu(1)-N(40) 88.18(12), N(21)-Cu(1)-N(41) 91.15(12), N(21)-Cu(1)-N(42) 91.55(12), N(40)-Cu(1)-N(41) 164.14(13), N(40)-Cu(1)-N(42) 96.13(14), N(41)-Cu(1)-N(42) 99.72.

Teller distortion. The copper centre is displaced from the basal plane slightly towards the axial thiocyanate, with apical-basal angles of 99.72(14) (N41-Cu1-N42), 96.13(14) (N40-Cu1-N42), 95.45(12) (N1-Cu1-N42) and 91.55(12)° (N21-Cu1-N42). The empty site which would complete an octahedral donor set has a weak (3.358 Å) interaction to the hydrogen bonded thiocyanate of an adjacent complex. The extended structure results from the hydrogen bonding of an amine proton to the terminal sulfur of the thiocyanate of an adjacent copper unit. The hydrogen bonding extends as a zigzag one-dimensional polymer along the *y*-axis. Examination of the packing in the *yz* plane reveals that the one-dimensional polymers pack together in such a way as to mimic the two-dimensional network of the previous two complexes (see Figure 2.9). The different planes in which the packing and network occur (*xy* and *yz* respectively) is due to the differing space groups of the two complexes – space group C2 constrains the *x*- and *z*-axes, while space group $P2_1$ follows standard crystallographic practices, in which the shorter axis is designated the *x*-axis.

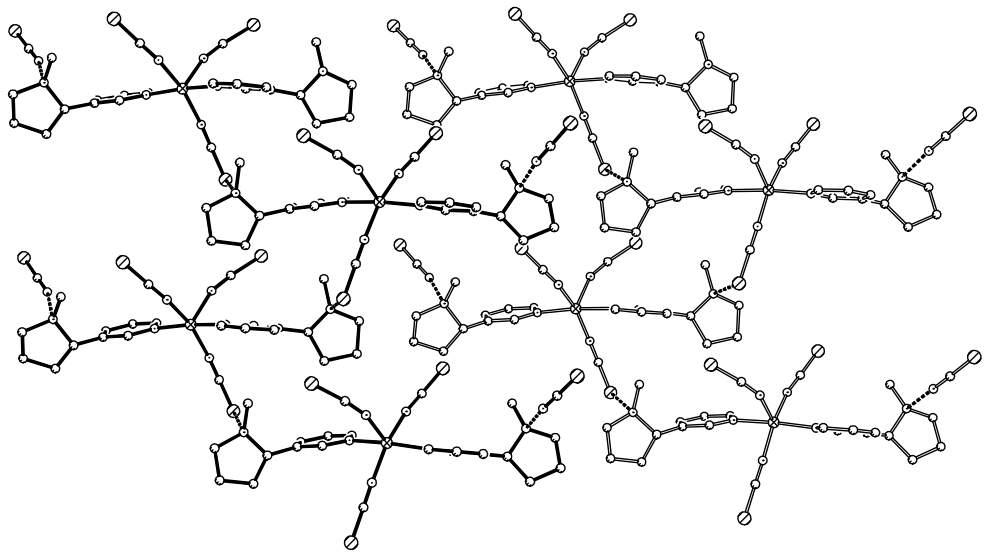


Figure 2.9: A packing diagram of complex 3 looking down the *x*-axis. On the left-hand side, with solid bonds, is a hydrogen bonded chain. On the right-hand side is another hydrogen bonded chain, which demonstrates how the two chains pack together, similar to the two-dimensional networks of the earlier complexes.

Structure 4

Complex **4** crystallizes in the monoclinic space group C2, as a 2:1 ligand:metal complex. Similar to structures **1** and **2**, hydrogen bonding to adjacent cadmium units extends to a two-dimensional (4,4) network in the *xy* plane. The asymmetric unit consists of a cadmium centre located on the 2-fold rotation axis, coordinated to a nicotine molecule via the pyridine nitrogen, and coordinated to two thiocyanate anions, one via the nitrogen terminus and one via the sulfur terminus. The larger size of the (second row transition metal) cadmium atom means that there is space for the larger sulfur donor to coordinate (see Figure 2.10), a difference from the smaller metals in the previous complexes. In the same manner as the structures of **1** and **2**, generation of the symmetry equivalent thiocyanates and nicotine units reveals the octahedral geometry of the complex. The charge balance is again accounted for by protonation of the nicotine molecules at the amine nitrogens. The hydrogen bonding network is similar to that of **1** and **2**, but with hydrogen bonding to the sulfur-bound thiocyanates, via the nitrogen terminus. Obviously this mode is not available in the other structures where the thiocyanates are all nitrogen-bound with only the sulfur terminus available for hydrogen bonding.

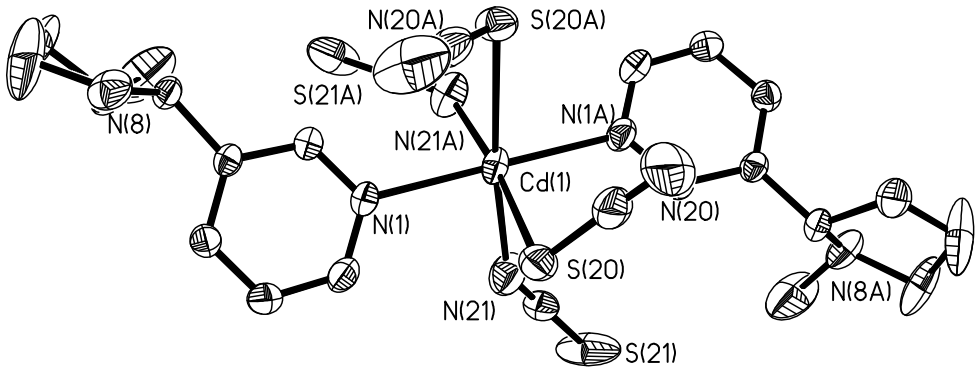


Figure 2.10: A perspective view of complex 4. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Cd(1)-N(1) 2.349(3), Cd(1)-S(20) 2.7479(13), Cd(1)-N(21) 2.302(5), N(1)-Cd(1)-N(1A) 178.1(3), N(1)-Cd(1)-S(20) 85.72(12), N(1)-Cd(1)-S(20A) 95.54(12), N(1)-Cd(1)-N(21) 90.69(18), N(1)-Cd(1)-N(21A) 88.06(18), S(20)-Cd(1)-S(20A) 95.19(6), S(20)-Cd(1)-N(21) 84.98(13), S(20)-Cd(1)-N(21A) 173.77(14), N(21)-Cd(1)-N(21A) 95.5(3).

Structure 6

Complex **6** crystallizes in the monoclinic space group C2, and has a structure very similar to that of the previous complexes that crystallized in this space group (see Figure 2.11). The quality of the crystals was such that initially the structure could only be solved in triclinic space group P1 and the correct higher symmetry space group and crystal system could not be determined. The initial cell used to solve the crystal structure was anorthic, although it was apparent from the structure that the complex should be isomorphous with the earlier structures. Eventually a monoclinic cell was found, and the structure solved in space group C2. When compared to other complexes in this series, the unit cell is slightly, but significantly, smaller (see Table 2.1). The effect of this on the structure of the complex is observed in the packing effects; there is an additional hydrogen bond to the thiocyanate of an adjacent molecule. This hydrogen bond does not affect the overall packing, which remains the same (see Figure 2.12), but does affect the description of the network. The network can now be described as a (2,8)

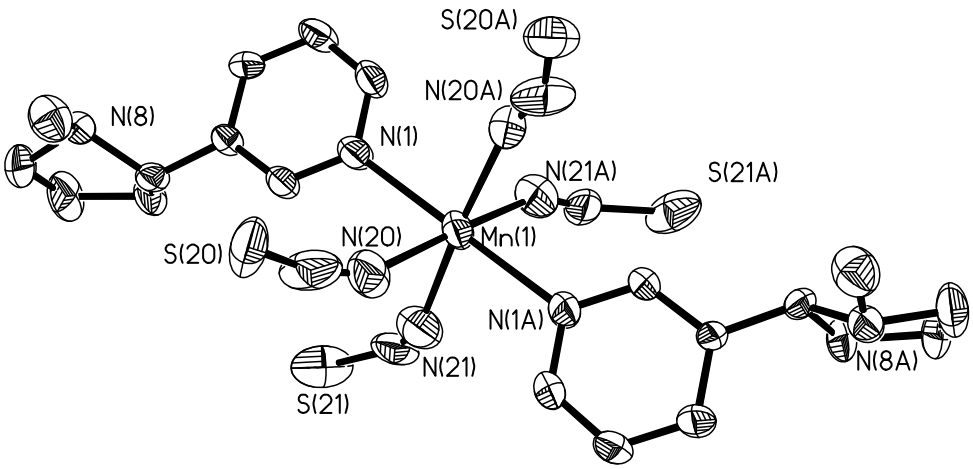


Figure 2.11: A perspective view of complex 6. Hydrogen atoms and disordered sulfur atoms of thiocyanates are omitted for clarity. Selected bond lengths (Å) and angles (°): Mn(1)-N(1) 2.292(6), Mn(1)-N(20) 2.150(12), Mn(1)-N(21) 2.220(12), N(1)-Mn(1)-N(1A) 179.2(6), N(1)-Mn(1)-N(20) 86.9(3), N(1)-Mn(1)-N(20A) 92.6(3), N(1)-Mn(1)-N(21) 88.9(4), N(1)-Mn(1)-N(21A) 91.7(4), N(20)-Mn(1)-N(20A) 96.0(6), N(20)-Mn(1)-N(21) 89.5(4), N(20)-Mn(1)-N(21A) 174.3(5), N(21)-Mn(1)-N(21A) 85.0(6).

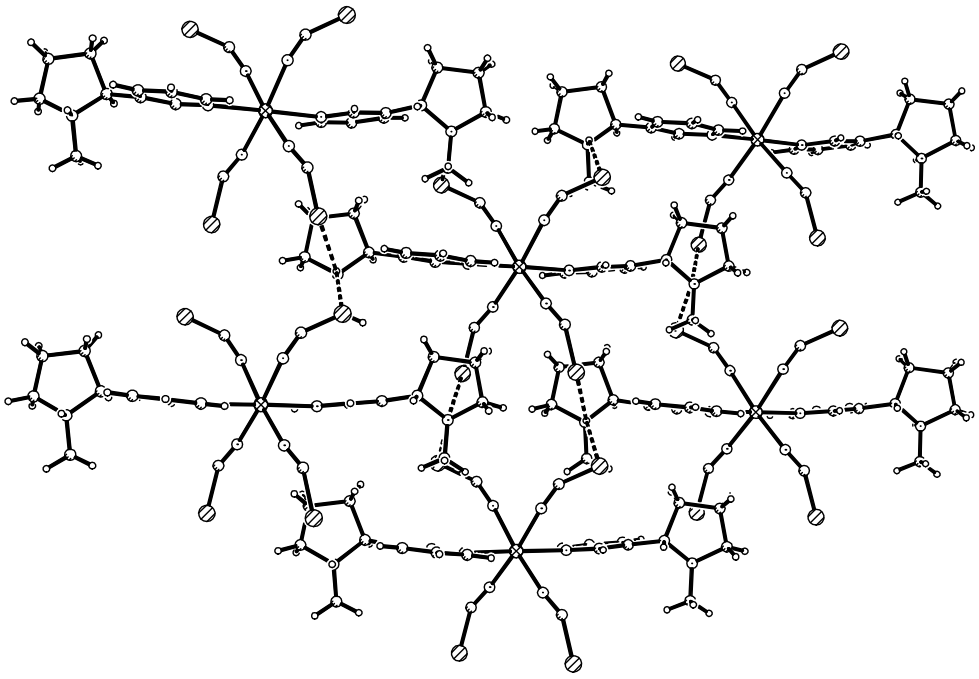


Figure 2.12: A packing diagram of complex 6 looking down the *z*-axis. The additional hydrogen bonds change the description of the network, but do not change the overall packing of the structure.

network, as opposed to the (4,4) network, which describes the previous complexes.

Comparison of the $M(SCN)_4(Nicotine.H)_2$ Series

This series of compounds can be readily compared and contrasted in a number of different ways; some of these comparisons have been noted above for the individual compounds. One section not fully explored previously is the comparison of the unit cell parameters of the different complexes (see Table 2.1). Comparison of these parameters reveals a number of features which can be explained or related to features within the structures themselves. Overall consideration of the unit cell lengths reveals, unsurprisingly, that they are all of similar dimensions. The two “most similar” structures, those of **1** and **2**, have

	a (Å)	*b* (Å)	*c* (Å)	*β* (°)	V (Å^3)	R_1 (%)
1	19.059(9)	10.772(5)	7.434(3)	107.09(3)	1458.9(11)	2.63
2	18.94(2)	10.805(13)	7.435(9)	106.88(4)	1456(3)	4.55
3†	18.236(6)	10.850(4)	7.478(2)	97.757(4)	1466.0(8)	4.00
4	19.505(4)	10.818(2)	7.4438(16)	106.141(2)	1508.8(5)	3.95
6	18.514(7)	10.606(4)	7.321(3)	93.943(3)	1434.2(9)	11.39
5	19.288(2)	10.757(1)	7.454(1)	107.260(1)	1476.9(5)	NA

Table 2.1: A comparison of the unit cell parameters of the $M(SCN)_4(Nicotine.H)_2$ series of compounds. The R_1 value is included for comparison. † The *a*- and *c*-axes for B6 have been inverted for ease of comparison.

extremely similar unit cell parameters, and will be used as a baseline for comparison and contrast.

Complex **3** has a shorter *a*-axis, but a less obtuse *β*-angle which means that the cell volume is slightly larger than that of the two baseline complexes. This difference can be attributed to this being the only complex of this series to crystallize in a space group other than C2 ($P2_1$). The structural difference of the complex, with a non-coordinated thiocyanate molecule, is the cause of this. It could be considered surprising that the cell parameters are still so similar, and that this complex maintains a packing arrangement so similar to the others in the series.

Complex **4** has a longer *a*-axis, and larger cell volume than the baseline complexes. This is due to the use of a (larger) metal, as opposed to the first row transition metals used for the baseline complexes. As noted above, this leads to one of the two thiocyanates, in the asymmetric unit, coordinated via the sulfur terminus as opposed to the nitrogen terminus. Again, this change does not significantly alter the overall packing of the complex, which is almost identical to that of the baseline complexes. An interesting feature is that when both sulfur and nitrogen termini of thiocyanate are available as hydrogen-bond acceptors, the nitrogen is bonded in preference.

Complex **6** is smaller in all dimensions, with a similar *β*-angle when compared with the baseline complexes. This is unsurprising when the structure is taken into account; the increased intermolecular interactions (an increased number of hydrogen bonds), makes the packing of this complex tighter, hence the reduced size of the unit cell. For this series, the overall packing is still extremely close to that of the baseline complexes.

Although the cell determination of **5** was of high quality, and the data were highly internally consistent (post absorption correction R_{int} of 2.13%), no solution could be obtained, probably due to some sort of twinning. Simple examination of the unit cell parameters shed little light beyond the obvious on the nature of the structure. The parameters are consistent with a complex closely related to the previous ones, however, the parameters are larger than those for both complexes **6** (manganese) and **1** (cobalt), which reside to either side of **5** (iron) in the periodic table. This indicates that there is some sort of structural variation, in all probability not yet explored in the previous complexes. One possibility, consistent with the red colour of the crystals, is that only a single nicotine molecule is protonated, and the iron exists in the Fe(III) oxidation state.

Another feature that can be compared between different complexes in this series is the relative orientation of the pyrrolidine ring with respect to the pyridine ring. A related detail is the relative conformation of the methyl group; whether a *cis* or *trans* relationship to the pyridine ring exists. Earlier work by Whidby and co-workers, on the basis of computational work, NMR and one X-ray crystal structure, as well as some knowledge of related systems, concluded that there is a perpendicular relationship between the pyrrolidine and pyridine rings[35, 36] and that the methyl group had a *trans* relationship to the pyridine ring.[37] If we compare the orientation of the nicotine rings amongst this series, by overlaying the nicotine molecules from the five different complexes for which crystal structures were obtained, we can see that all the nicotine molecules have very similar geometry (see Figure 2.13). This can further be compared to the perpendicular orientation suggested by Whidby and co-workers, and it is

apparent that the original conformation proposed is very close to that observed in this series of compounds in the solid state (see Figure 2.14).

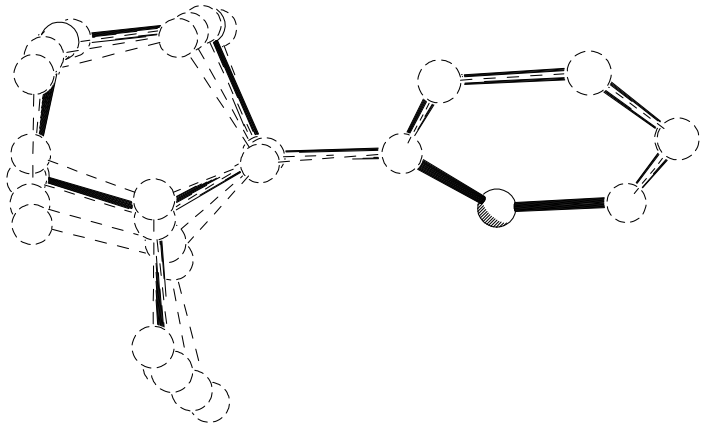


Figure 2.13: A representation of how the different nicotine molecules from complexes 1, 2, 3, 4 and 6 compare. All complexes have been fitted with the pyridine ring in a constant position, showing the difference in relative configuration of the pyrrolidine rings.

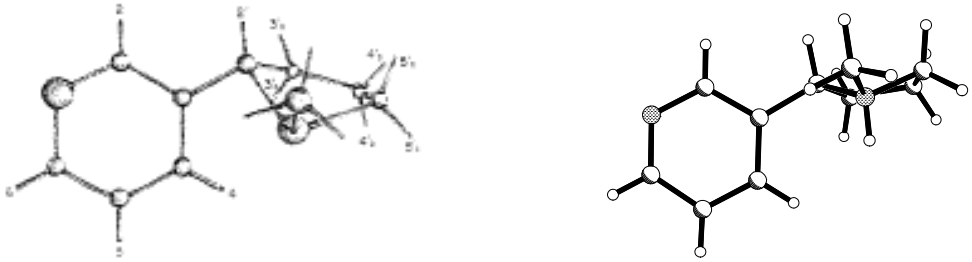


Figure 2.14: A comparison of the original conformation proposed by Whidby and co-workers (left), and the conformation of the nicotine molecule in complex 1 (right)

2.2.2 Complexes of Nicotine: Silver Complexes

Silver(I) has been used extensively for the synthesis of coordination and metallosupramolecular complexes, both by this group and others.[8, 21, 38, 39] Silver(I) has a wide variety of coordination modes, ranging from 2- to 6-coordinate, and has flexible coordination geometry. For these reasons it was attractive as a metal centre in this study.

Investigation of the coordination chemistry of nicotine with silver(I) involved the reactions with various silver(I) salts. Reaction of one equivalent of nicotine with one equivalent of silver nitrate, followed by the slow diffusion of diethyl ether into the reaction mixture resulted in **8** depositing from solution as crystals suitable for X-ray crystallography in a yield of 56%. Analysis of this complex by ^{1}H-NMR revealed contact induced shifts for the aromatic protons. Analysis by electrospray mass-spectroscopy showed the major component in solution was a 1:1 silver(I):nicotine species, although more complex mixtures of silver(I), nicotine, nitrate and acetonitrile (the solvent used for the procedure) were observed. The crystals were suitable for X-ray crystallography, and the structure of the complex was determined by this method.

Further investigation into the coordination of nicotine with silver(I) involved both different ratios of silver:nicotine and the use of different counter ions. Reaction of three equivalents of nicotine with one equivalent of silver nitrate under the same conditions as for synthesis of the 1:1 complex yielded a crystalline complex suitable for X-ray crystallography. Elemental analysis revealed a 1:2 silver:nicotine ratio, and complex **9** was produced in a yield of 74%. Analysis of the complex by ^{1}H-NMR again revealed contact induced shifts, although smaller that those of the 1:1 complex. The structure of the complex was determined by X-ray crystallography, and the 1:2 silver:nicotine ratio confirmed.

The third silver-nicotine complex investigated involved the use of a different counter ion. Reaction of a 1:1 mixture of silver tetrafluoroborate and nicotine under the same conditions as the previous complexes resulted in a crystalline product suitable for X-ray crystallography. The complex (**10**) was synthesized in 72% yield. Elemental analysis of this complex showed a 1:1 silver tetrafluoroborate:nicotine ratio. It is believed that solvent is lost from the complex in the process of analysis, as the crystal structure revealed solvent molecules in the complex.

The contact induced shift of proton resonances in the silver-nicotine complexes is smaller than that with more inert metal centres (see Table 2.2). This is

Molecule	δ(H2) ppm	δ(H4) ppm	δ(H5) ppm	δ(H6) ppm
Nicotine	8.61	7.40	7.81	8.54
8	8.70	7.56	7.99	8.55
9	8.69	7.36-7.40	7.82-7.85	8.54
8-nicotine	+0.09	+0.16	+0.18	+0.01
9-nicotine	+0.08	-0.02 (av.)	+0.025 (av.)	+0.00

Table 2.2: A comparison of the chemical shifts of the pyridine ring protons of nicotine, 8 and 9.

probably due to the weak silver-nicotine bond and a rapid equilibrium between coordinated and non-coordinated nicotine molecules.

Structure of 8

Complex **8** is a three-dimensional network, with both the nicotine molecule and the nitrate counter ion acting as bridges between different silver(I) atoms. The complex crystallizes in the orthorhombic space group $P2_12_12_1$. The deceptively

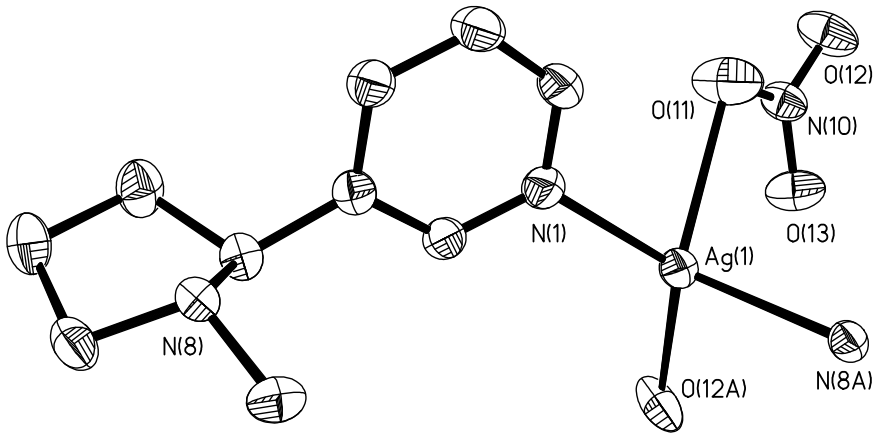


Figure 2.15: The coordination sphere of 8. Atoms N(8A) and O(12A) are symmetry equivalents of N(8) and O(12) respectively. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Ag(1)-N(1) 2.301(2), Ag(1)-N(8A) 2.381(2), Ag(1)-O(11) 2.579(2), Ag(1)-O(12A) 2.451(2), N(1)-Ag(1)-O(11) 85.22(6), N(1)-Ag(1)-N(8A) 125.35(6), N(1)-Ag(1)-O(12A) 127.85(7), O(11)-Ag(1)-N(8A) 102.81(7), O(11)-Ag(1)-O(12A) 123.47(7), N(8A)-Ag(1)-O(12A) 92.48(7).

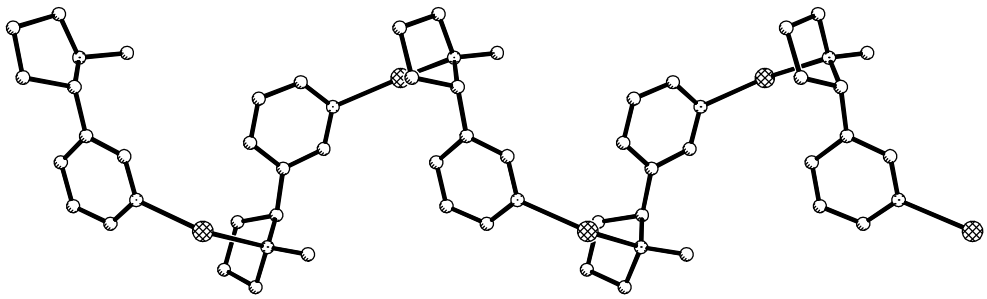


Figure 2.16: A perspective view of the silver-nicotine-silver motif along the *z*-axis. Hydrogens and nitrate counter ions have been omitted for clarity.

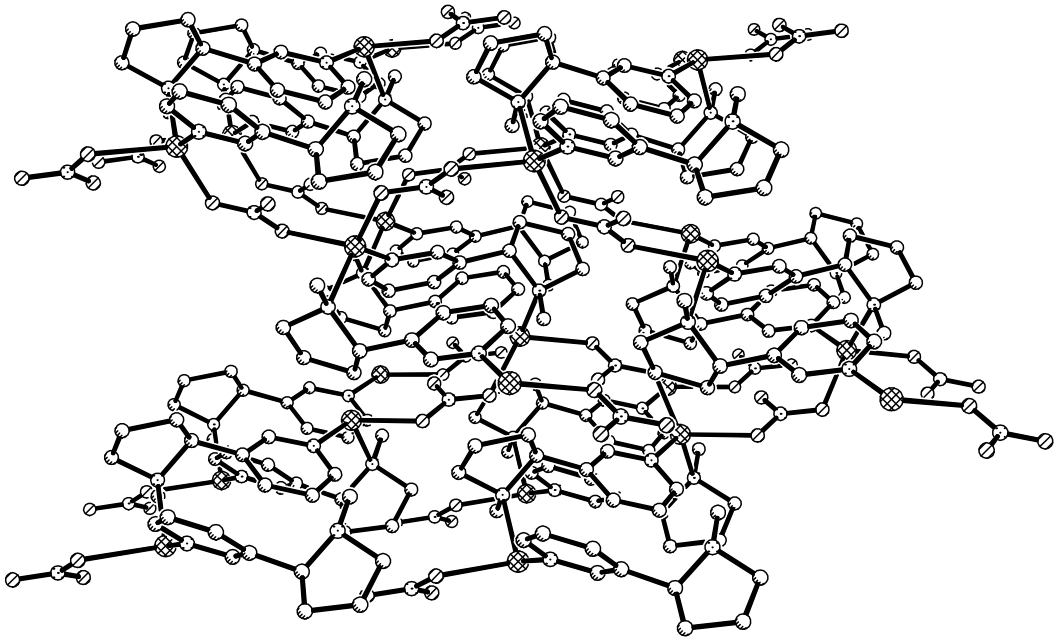


Figure 2.17: The three-dimensional coordination network of 8.

simple asymmetric unit consists of a single silver centre coordinated to a nicotine through the pyridine nitrogen, and to a nitrate through an oxygen. The coordination sphere (see Figure 2.15) of the silver atom is completed by coordination of a symmetry equivalent nicotine through the amine nitrogen, and the oxygen of a symmetry equivalent nitrate. The geometry around the silver atom is a distorted tetrahedron, with angles ranging from 85.22(6) to 127.85(7)°. The silver-nicotine-silver motif forms a one-dimensional helical polymer,

propagating via the 2_1 screw axis in the *z*-direction (see Figure 2.16). These polymers are also directional, as the nicotine is asymmetric, so the two ends of the polymer are distinct from each other. A consequence of the space group in which the complex crystallized is that polymers going in both directions coexist in the same crystal. These one-dimensional chains are cross-linked by the nitrates to form the three-dimensional network (see Figure 2.17). Pairs of silver atoms bridged by the nicotine molecules are separated by 7.886 Å, while those bridged by nitrate anions are 5.715 Å apart.

Structure of 9

Complex **9** crystallizes as a one-dimensional coordination polymer in the monoclinic space group $P2_1$, with one of two nicotine molecules acting as the bridging ligand between silver centres. The asymmetric unit consists of a silver centre coordinated by two nicotine molecules via pyridine nitrogens, as well as an oxygen coordinated nitrate. The coordination sphere is completed by the symmetry equivalent amine nitrogen of one of the nicotine molecules, while the other remains hypodentate (see Figure 2.18). The geometry around the silver centre is again distorted tetrahedral, with angles ranging from 91.01(7) to 120.14(8)°, a less severe distortion than in complex **8**. The silver-nicotine-silver motif propagates via the 2_1 screw axis in the *y*-direction. Again this is a helical, directional coordination polymer, and when compared to the silver-nicotine-silver motif from complex **8** (ignoring additional ligands) is almost identical (see Figure 2.19). The distance between silver atoms bridged by nicotine molecules in this case is 8.019 Å. A consequence of the space group in this case is that the entire crystal consists of polymer chains all having the same direction, so overall the crystal is unidirectional. The pendant nicotine molecules interdigitate into cavities within the adjacent polymer chain in the *z*-direction (see Figure 2.20).

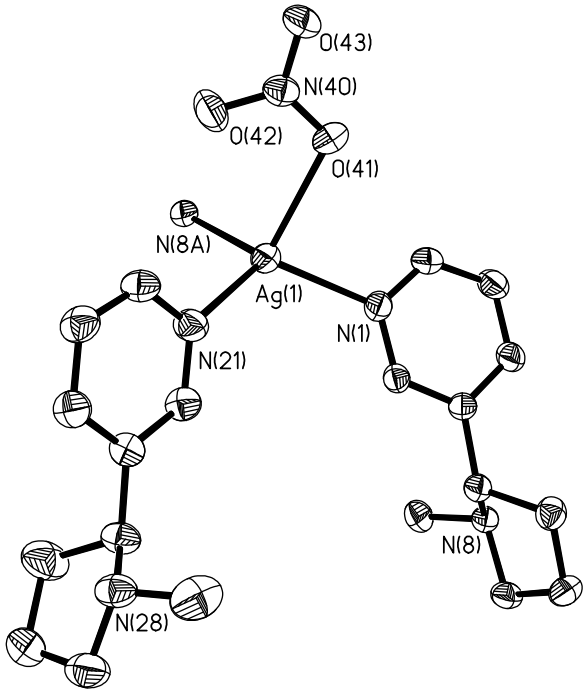


Figure 2.18: The coordination sphere of the silver centre in 9. N(8A) is the symmetry equivalent of N(8). Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Ag(1)-N(1) 2.323(2), Ag(1)-N(21) 2.298(2), Ag(1)-N(8A) 2.405(2), Ag(1)-O(41) 2.500(2), N(1)-Ag(1)-N(21) 120.14(8), N(1)-Ag(1)-N(8A) 117.93(7), N(1)-Ag(1)-O(41) 91.01, N(21)-Ag(1)-N(8A) 106.76(8), N(21)-Ag(1)-O(41) 116.05(8), N(8A)-Ag(1)-O(41) 103.19(7).

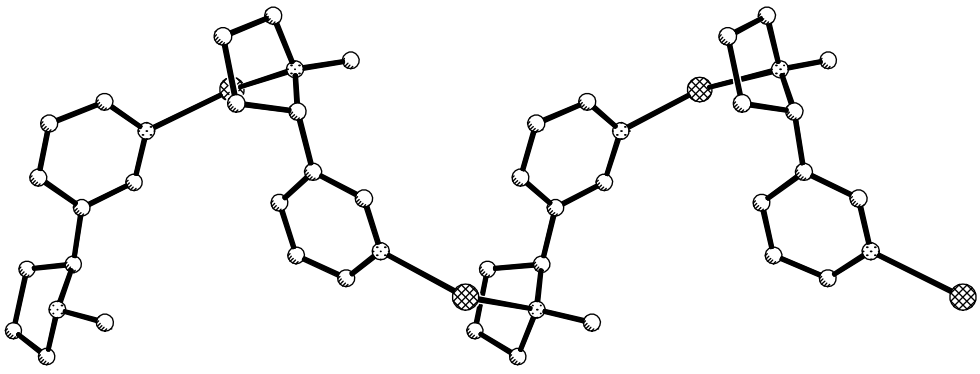


Figure 2.19: A perspective view of the silver-nicotine-silver motif along the *y*-axis. Hydrogens, nitrate counter ions, and the pendant nicotine molecules have been omitted for clarity.

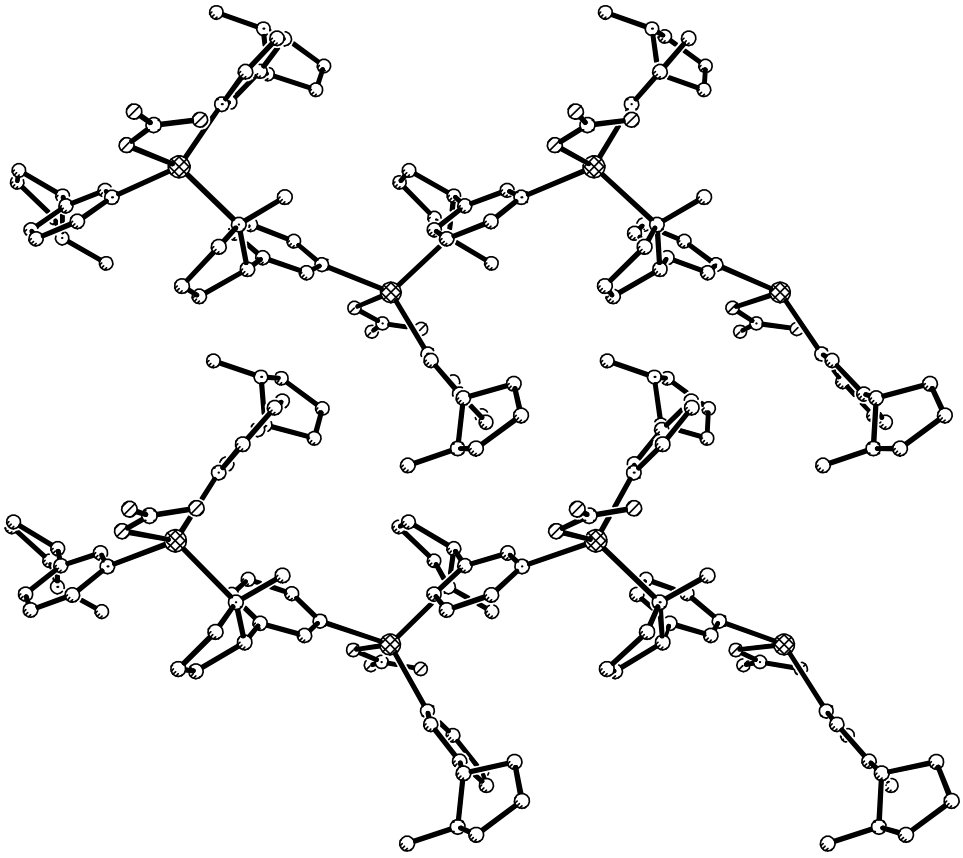


Figure 2.20: A view of the packing in the *yz*-plane, showing how the pendant nicotines interdigitate.

Structure of 10

Complex **10** crystallizes in the monoclinic space group $P2_1$, as a one-dimensional coordination polymer, in which nicotine acts as a bridge between silver centres. The asymmetric unit of the complex consists of a silver centre coordinated to two acetonitrile molecules and a nicotine via the pyridine nitrogen, as well as a non-coordinated, disordered, tetrafluoroborate counter ion (see Figure 2.21). The coordination sphere of the silver is completed by the amine nitrogen of a translationally related nicotine molecule. The geometry around the silver centre is again distorted tetrahedral, with angles ranging from 86.5(1) to 127.9(1)°, a similar distortion to **8**. The silver-nicotine-silver motif propagates along the *x*-direction, with a silver-silver distance of 7.602 Å, the length of the *a*-axis. The polymer chains in this complex are generated by translation, which

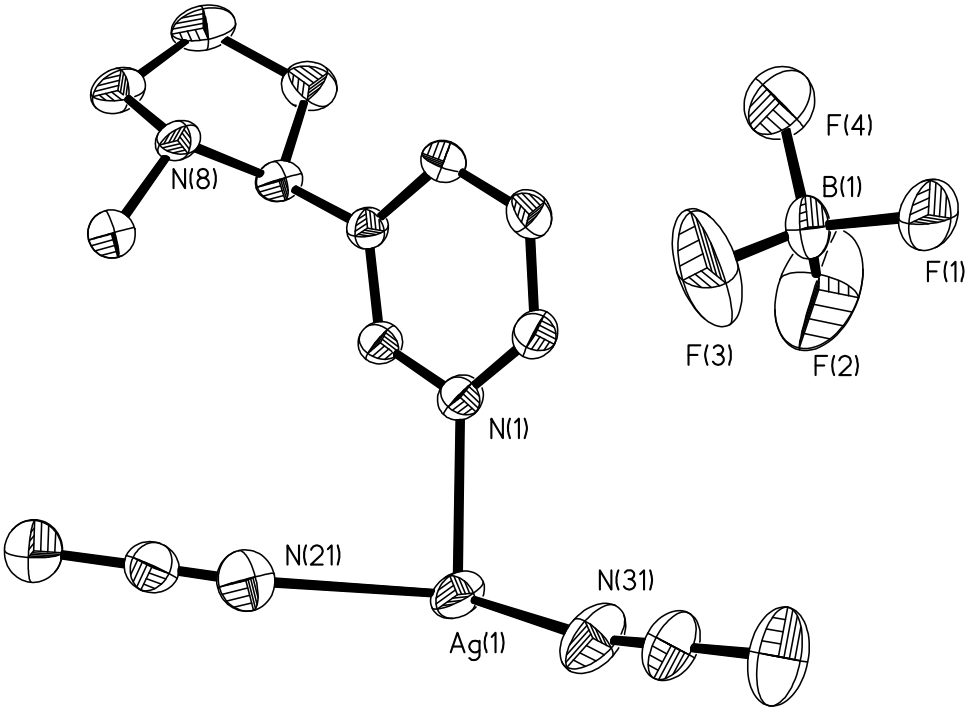


Figure 2.21: The asymmetric unit of 10. Hydrogen atoms and the minor component of the tetrafluoroborate counter ion are omitted for clarity. Selected bond lengths (Å) and angles (°): Ag(1)-N(1) 2.334(3), Ag(1)-N(21) 2.572(4), Ag(1)-N(31) 2.329(3), Ag(1)-N(8A) 2.326(3), N(1)-Ag(1)-N(21) 86.49(11), N(1)-Ag(1)-N(31) 99.70(11), N(1)-Ag(1)-N(8A) 127.93(9), N(21)-Ag(1)-N(31) 113.75(13), N(21)-Ag(1)-N(8A) 94.54(12), N(31)-Ag(1)-N(8A) 126.3(1).

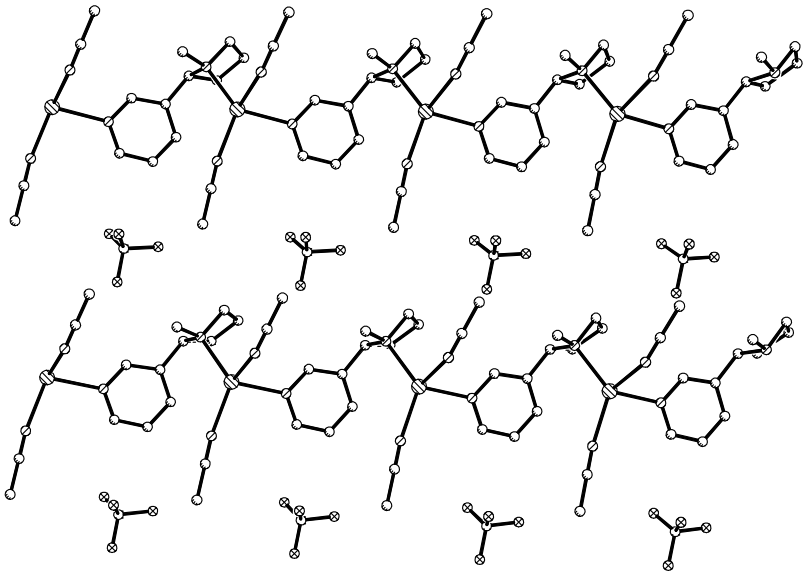


Figure 2.22: The packing of complex 10 in the *xz*-plane. Hydrogens and the minor component of the counter ion have been omitted for clarity.

differs to those in **8** and **9**, which are generated by a screw axis. Again, this polymer is directional, due to the asymmetric nature of the bridging ligand. Polymer chains going in opposite directions exist in each crystal, so overall they are not directional (unlike **9**). The tetrafluoroborate counter ions occupy the voids between polymer chains (see Figure 2.22).

Comparison of Silver Complexes

As with the previous section, there are further comparisons that can be made between the different complexes. In this case comparing the overall cell characteristics does not reveal any trends, however comparison of the conformation of the different nicotine molecules is still useful. The four nicotine molecules from three different structures all have very similar relative ring conformations (see Figure 2.23). Again this conformation is very similar to that proposed originally by Whidby and co-workers (see Section 2.2.1 for more details). The three complexes described in this section were published together under the title “Chiral Heterocyclic Ligands. XI. Self-assembly and X-Ray Crystal Structures of Chiral Silver Coordination Polymers of (*S*)-(-)-Nicotine”.[40]

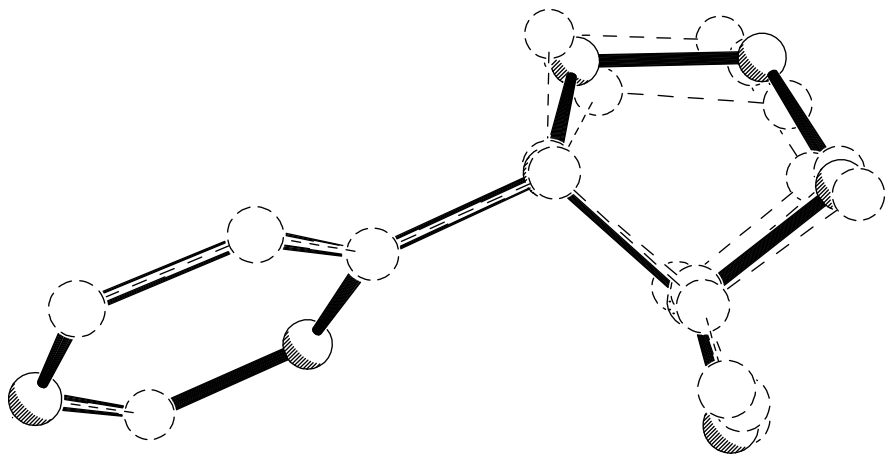


Figure 2.23: The relative conformations of the 4 different nicotine molecules in complexes 8, 9 and 10. Pyridine rings have been fitted as being coincident to compare the relative conformations of the pyrrolidine rings of different molecules.

2.2.3 Complexes of Nicotine: Other Metal Complexes

A number of other coordination complexes were synthesized in the course of this project, for a variety of reasons. Complex **7**, for example, was synthesized as a by-product in the synthesis of another complex (**2**).

Ruthenium complexes are widely studied for a variety of reasons. They have been studied extensively in this group,[39, 41] with their electrochemical and structural properties being of interest. Ruthenium tris(bipyridyl) complexes have inherent chirality, and are generally synthesized as a mixture of two enantiomers. Synthesis of a bis-nicotine adduct would provide the complex as a mixture of two diastereoisomers, which could potentially be separated, and could have interesting properties. This provided the incentive for the synthesis of **11**.

A method of avoiding the inherent chirality of the ruthenium bis(bipyridyl) system is to use a ruthenium terpyridine bipyridine system; in this case the central metal atom is achiral, and all of the chirality comes from the monodentate substituent. The use of nicotine (which is supplied as a single enantiomer) in the synthesis of such a complex (**12**) would result in a chiral ruthenium complex which is achiral at the metal centre.

Synthesis of a complex in which nicotine acted only as a monodentate ligand, and was not protonated was targeted. One method of achieving such geometry is the use of a square-planar metal centre coordinated to a terpyridine, leaving only one possible coordination site. This approach led to **13**.

Synthesis of the Complexes

Complex **7** was synthesized as detailed in Section 2.2.1, with a yield of 18%. A number of crystals were trialled for X-ray crystallography before a suitable one was found, however this crystal was still of low quality, and the X-ray crystal structure was also of low quality.

An attempt was made to synthesize a ruthenium bis-bipyridyl, bis-nicotine complex (**11** – see Figure 2.24). Bis(2,2'-bipyridine)dichlororuthenium(II) was reacted with several equivalents of nicotine and the product was isolated with a yield of 56% following workup. Examination of the complex by ^{1}H-NMR showed that only one chloride had been displaced and the mono-chloro, mono-nicotine complex (**12**) had been synthesized. Attempts were made to synthesize the bis-nicotine complex via removal of the chloride with silver salts, as well as using a ruthenium complex with more readily replaced counter ions (in this case triflate). Neither method resulted in the desired bis-nicotine complex **11**. Following the synthesis of the original complex, a microwave reactor became available (a domestic microwave adapted for chemical synthesis). The synthesis of **11** was attempted via this method as well. Bis(2,2'-bipyridine)dichlororuthenium(II) and several equivalents of nicotine were dissolved in ethylene glycol, with a drop of water added. The solution was heated by ten consecutive exposures in the microwave reactor for 30 seconds each at 600 watts, interspersed by careful swirling of the solution. Initial examination of the product by ^{1}H-NMR following workup indicated that **12** had again been synthesized, so this method was pursued no further. Numerous attempts failed to recrystallize this complex.

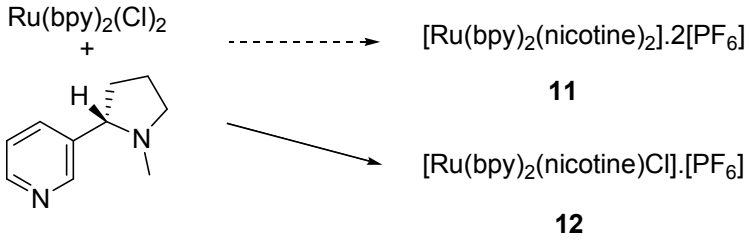


Figure 2.24: The attempted synthesis of 11, which results in 12.

After the attempted synthesis of **11**, it was decided to attempt the synthesis of a similar complex that would not possess any chlorides, namely a ruthenium terpyridine bipyridine complex. (2,2'-Bipyridine)chloro(2,2':6',2"-terpyridine)ruthenium(II) hexafluorophosphate was synthesized by literature methods,[42] with a yield of 53%. This precursor was reacted with nicotine in 1:1 ethanol:water, and isolated in a manner identical to **12**. Purification by column chromatography provided an orange solid. Examination of this solid by ^{1}H-NMR

confirmed the identity as the desired product (**13**). Numerous attempts failed to recrystallize this complex.

After the successful synthesis of **13**, in an attempt to crystallize a structure in which the nicotine molecule acts as a monodentate ligand, synthesis of a copper-terpyridine-nicotine complex (**14**) was attempted. Hexa(aqua)copper(II) perchlorate was reacted with a slight excess of nicotine and subsequently with half that amount of 2,2':6',2"-terpyridine. The solid formed was removed by filtration, and the desired product obtained in a yield of 53% by the slow diffusion of diethyl ether into the filtrate.

Structure of 7

Complex **7** crystallizes in the monoclinic space group $P2_1$, as a 4:1 ligand:metal complex. The asymmetric unit contains two complexes, which each consist of a central octahedral nickel atom coordinated to four nicotine molecules through the

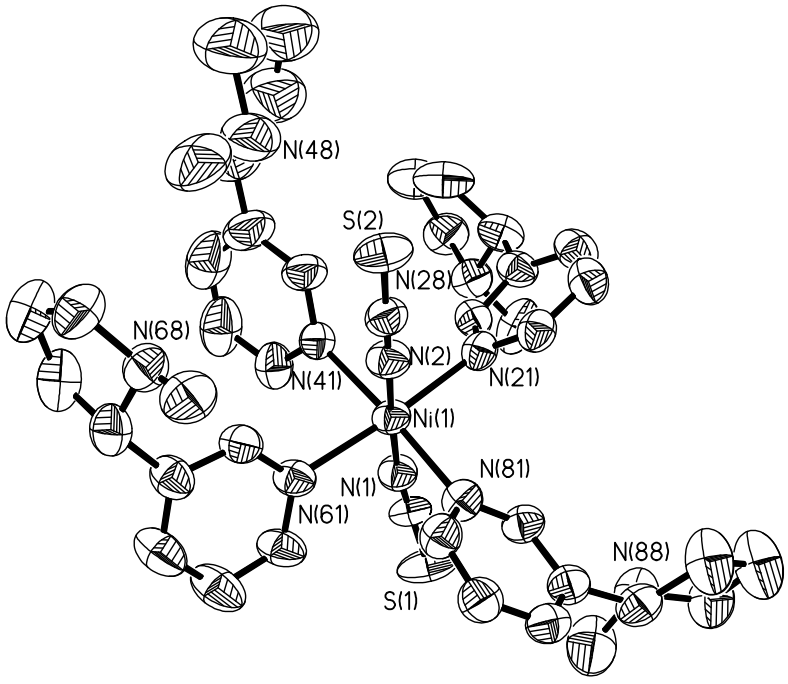


Figure 2.25: A perspective view of a single molecule of complex 7. Hydrogen atoms are omitted for clarity.

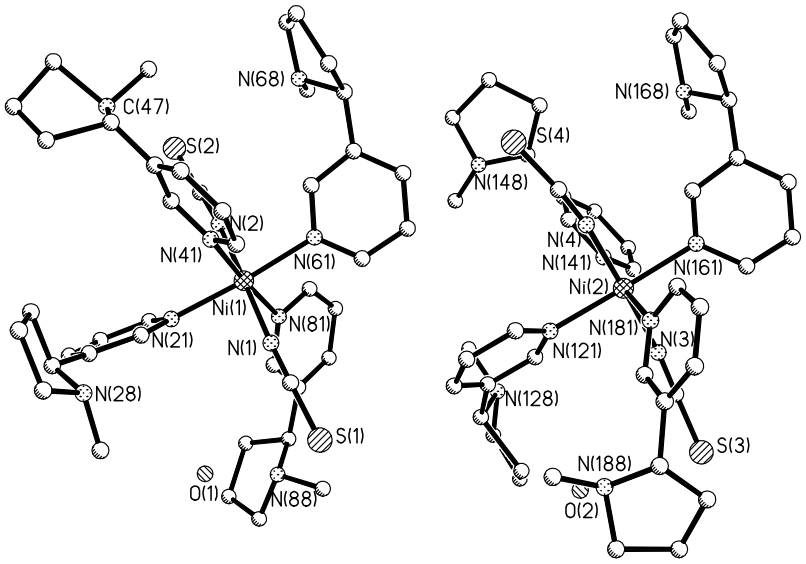


Figure 2.26: A perspective view of the contents of the asymmetric unit of complex 7. Hydrogen atoms and the minor component of the disordered thiocyanate sulfur atom are omitted for clarity. Selected bond lengths (Å), and angles (°): Ni(1)-N(1) 2.044(6), Ni(1)-N(2) 2.051(6), Ni(1)-N(21) 2.115(5), Ni(1)-N(41) 2.158(5), Ni(1)-N(61) 2.130(5), Ni(1)-N(81) 2.141(5), N(1)-Ni(1)-N(2) 177.6(3), N(1)-Ni(1)-N(21) 90.9(2), N(1)-Ni(1)-N(41) 91.6(3), N(1)-Ni(1)-N(61) 91.1(2), N(1)-Ni(1)-N(81) 88.4(2), N(2)-Ni(1)-N(21) 88.4(2), N(2)-Ni(1)-N(41) 91.6(3), N(2)-Ni(1)-N(61) 89.8(2), N(2)-Ni(1)-N(81) 89.3(3), N(21)-Ni(1)-N(41) 90.3(2), N(21)-Ni(1)-N(61) 175.6(2), N(21)-Ni(1)-N(81) 93.3(2), N(41)-Ni(1)-N(61) 85.7(2), N(41)-Ni(1)-N(81) 176.4(2), N(61)-Ni(1)-N(81) 90.7(2), Ni(2)-N(3) 2.056(6), Ni(2)-N(4) 2.039(6), Ni(2)-N(121) 2.119(5), Ni(2)-N(141) 2.131(6), Ni(2)-N(161) 2.127(5), Ni(2)-N(181) 2.131(6), N(3)-Ni(2)-N(4) 176.9(3), N(3)-Ni(2)-N(121) 88.9(2), N(3)-Ni(2)-N(141) 91.2(2), N(3)-Ni(2)-N(161) 91.1(2), N(3)-Ni(2)-N(181) 87.9(2), N(4)-Ni(2)-N(121) 89.5(2), N(4)-Ni(2)-N(141) 91.5(2), N(4)-Ni(2)-N(161) 90.6(2), N(4)-Ni(2)-N(181) 89.6(2), N(121)-Ni(2)-N(141) 90.9(2), N(121)-Ni(2)-N(161) 177.1(3), N(121)-Ni(2)-N(181) 92.6(2), N(141)-Ni(2)-N(161) 86.2(2), N(141)-Ni(2)-N(181) 176.4(2), N(161)-Ni(2)-N(181) 90.3(2).

pyridine nitrogen in equatorial positions, with two thiocyanates coordinated through the nitrogen terminus in axial positions (see Figure 2.25 for an example of one molecule). Each complex has a half-occupied water molecule associated with it (see Figure 2.26 for the asymmetric unit), in an appropriate position to hydrogen bond to the amine nitrogen of one of the coordinated nicotine molecules; unfortunately the hydrogen atoms of the water molecules could not be located in the electron-density difference map, and so were not assigned in the structure. Beyond this possible hydrogen bond there are no further hydrogen

bonds in or between the molecules. The two molecules are related by a pseudo-*c*-glide plane; however the use of chiral substituents (nicotine) precludes this.[43] In each molecule the nicotine pyridines exhibit a propeller-like relationship around the central nickel atom. Interestingly, the pyrrolidine rings of the nicotine are not arranged in a typical alternating up-down-up-down arrangement with respect to each other and the equator. Instead they are arranged in an up-up-down-down fashion. The extended structure exhibits no notable intermolecular interaction between adjacent molecules, and the packing overall is unremarkable.

Comparison of the relative conformation of the nicotine molecules by overlaying shows that they all very similar (see Figure 2.27). Interestingly the relative position of the pyridine nitrogen is different in this structure, rotated 180° when compared to the position in previous complexes in this chapter. However the relative conformation of the two rings is still perpendicular.

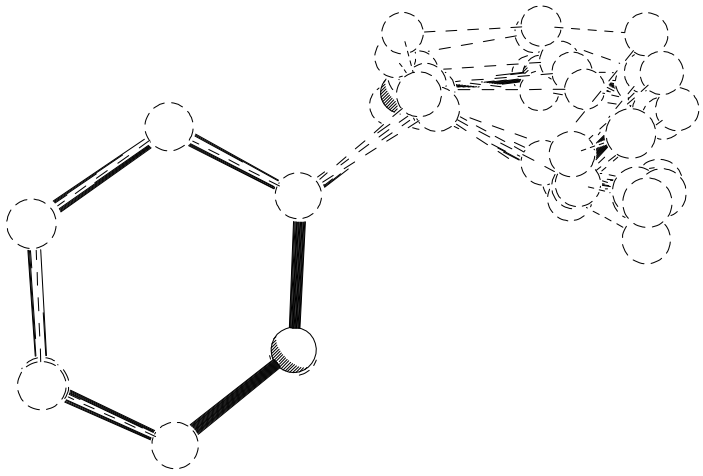


Figure 2.27: An overlay off the eight different nicotine molecules present in complex 7.

Structure of 14

Complex **14** crystallizes in the triclinic space group P1, as a discrete 1:1 ligand:metal complex. The asymmetric unit (see Figure 2.28) consists of two copper(II)-terpyridine-nicotine units, each with a square planar geometry. Both

units have a long copper-perchlorate bond in one axial site (2.424 and 2.458 Å for molecules 1 and 2 respectively) and a longer copper-perchlorate interaction in the second axial site (2.745 and 2.742 Å for molecules 1 and 2 respectively). The internal angles between adjacent pyridines of the terpyridines are less than the ideal right angle (ranging from 79.9(5) to 81.6(5)°) due to the constrained geometry of the molecule; consequently the angles between the nicotines and outer pyridines are greater than 90° (ranging from 97.6(5) to 101.5(5)°). The angles between the nicotines and outer pyridines are however exaggerated by

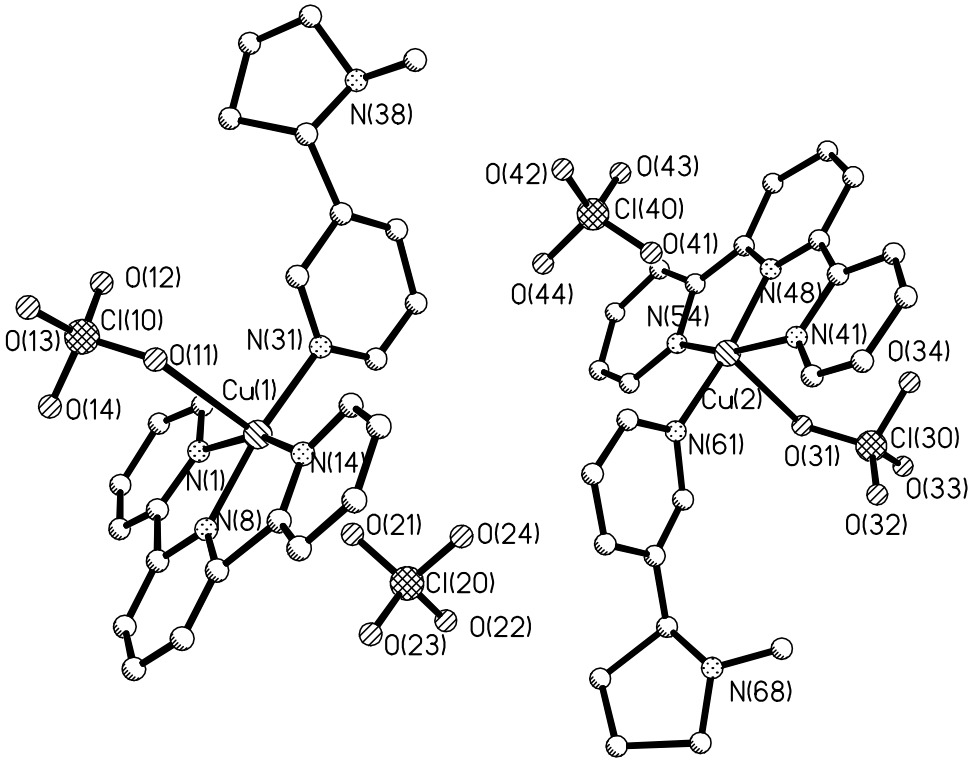


Figure 2.28: A perspective view of the asymmetric unit of complex 14. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Cu(1)-N(1) 2.074(13), Cu(1)-N(8) 1.924(12), Cu(1)-N(14) 2.100(12), Cu(1)-N(31) 2.026(11), Cu(1)-O(11) 2.424(11), N(1)-Cu(1)-N(8) 79.9(5), N(1)-Cu(1)-N(14) 160.1(5), N(1)-Cu(1)-N(31) 98.2(5), N(8)-Cu(1)-N(14) 80.2(5), N(8)-Cu(1)-N(31) 171.7(6), N(8)-Cu(1)-O(11) 91.3(5), N(14)-Cu(1)-N(31) 101.5(5), N(14)-Cu(1)-O(11) 86.6(4), N(31)-Cu(1)-O(11) 96.8(5), Cu(2)-N(41) 2.018(13), Cu(2)-N(48) 1.951(13), Cu(2)-N(54) 1.984(13), Cu(2)-N(61) 1.944(12), Cu(2)-O(31) 2.458(13), N(41)-Cu(2)-N(48) 81.4(5), N(41)- Cu(2)-N(54) 163.0(5), N(41)-Cu(2)-N(61) 97.6(5), N(41)-Cu(2)-O(31) 96.9(4), N(48)-Cu(2)-N(54) 81.6(5), N(48)-Cu(2)-N(61) 172.6(6), N(48)-Cu(2)-O(31) 93.1(5), N(54)-Cu(2)-N(61) 99.3(5), N(54)-Cu(2)-O(31) 83.6(4), N(61)-Cu(2)-O(31) 94.3(5).

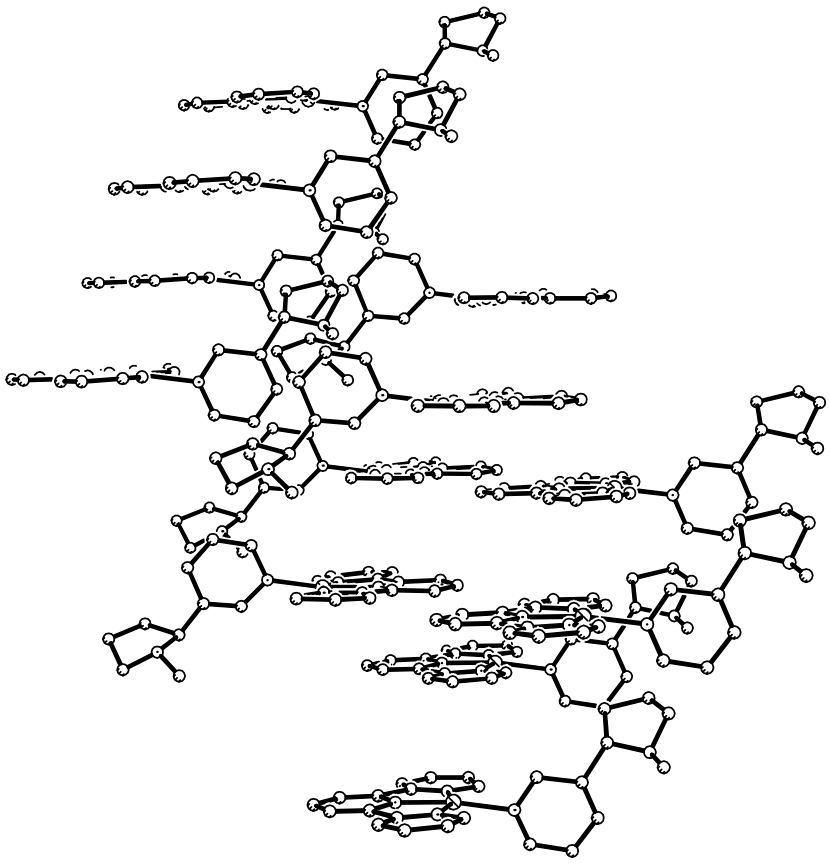


Figure 2.29: A packing diagram of complex 14. The interdigitation of the nicotine pyrrolidine groups can clearly be seen, while the limited π-stacking is less obvious.

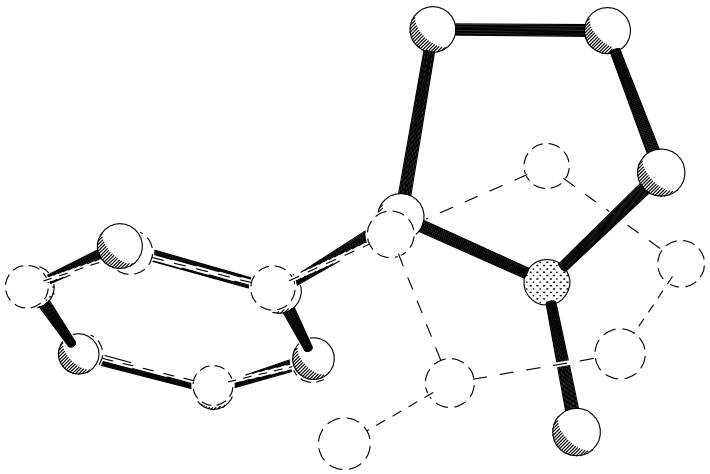


Figure 2.30: An overlay of the two different nicotine molecules in complex 14.

the slight out of plane position of the central copper atom (~0.09 and ~0.07 Å out of plane for molecules 1 and 2 respectively) – it is distorted towards the attached perchlorate anion, despite the Jahn-Teller lengthening of this bond. The two molecules in the asymmetric unit are related by a pseudo-inversion centre (see Figure 2.28); however, the complex cannot be solved in the space group P-1 as the use of a chiral substituent precludes this.[43] There are only a limited number of longer range effects in this structure which affect the packing: in the *y*-direction nicotine molecules interdigitate, while there is weak π-stacking between the terpyridines of adjacent molecules along the *z*- axis (see Figure 2.29). Unfortunately this complex exhibited poor crystal quality, and so the crystal structure could not be satisfactorily refined. Anisotropic refinement results in a small number of non-positive-definite atoms, as well as some with large thermal displacement factors, which do not represent any coherent disorder.

Comparison of the two nicotine molecules in the structure by overlaying the pyridine rings (see Figure 2.30), reveals that the two nicotine molecules have comparatively different relative conformations. Both molecules are still reasonably close to the conformation proposed by Whidby and co-workers, but packing effects have enforced a rotation, in opposite directions, resulting in an obvious difference between the two.

2.3 Complexes of Quinine

Syntheses of the Complexes

Complex **15** was synthesized by the reaction of quinine with copper(II) chloride in a 2:1 mixture of methanol and acetonitrile. Crystals suitable for X-ray crystallography formed overnight in a yield of 80%. The complex was analysed by elemental analysis to confirm the solid state structure. An attempt to analyse the solution state of the complex by mass-spectroscopy was inconclusive due to complete dissociation of the complex.

The analogous copper(II) bromide complex, **16** was synthesized in a similar manner as **15**, with a yield of 67%, and the same analysis performed. Again, attempts to probe the solution state of the complex by mass-spectroscopy were inconclusive due to dissociation of the complex.

Complex **17** was synthesized by the reaction of cobalt(II) chloride with quinine in methanol. Crystals suitable for X-ray crystallography were obtained overnight. After the structure was identified as closely related to previously published work (see below for details), no further analysis was attempted.

Structure of 15

Complex **15** crystallizes in the monoclinic space group $P2_1$, with one molecule in the asymmetric unit. The molecule consists of a Cu_2O_2 square, with each copper coordinated to both oxygen atoms of different quinine molecules. The coordination sphere of each copper atom is completed by a chloride counter ion, and a quinuclidine nitrogen from one of the quinine molecules; this means that each copper atom has a monodentate quinine and a chelating bidentate quinine coordinated (see Figure 2.31). The asymmetric unit is completed by two solvent

acetonitrile molecules. One of these acetonitrile molecules has a long (2.988 Å) interaction to Cu(1), while the other has no intermolecular interactions. The copper-copper distance in this complex is 2.9644(10) Å, too long to be considered a bond, but probably some sort of longer range interaction would exist. The geometry of the copper atoms is distorted square planar, with angles between adjacent substituents ranging from 75.64(11) to 100.83(10)°, the distortion imposed by the 5-membered chelate ring on the bidentate quinine molecule. There is a pseudo-2-fold rotation axis in the middle of the Cu_2O_2 square. However, the quinuclidine section of the quinine molecules are not truly coincident with respect to this axis. The acetonitriles also do not conform to the

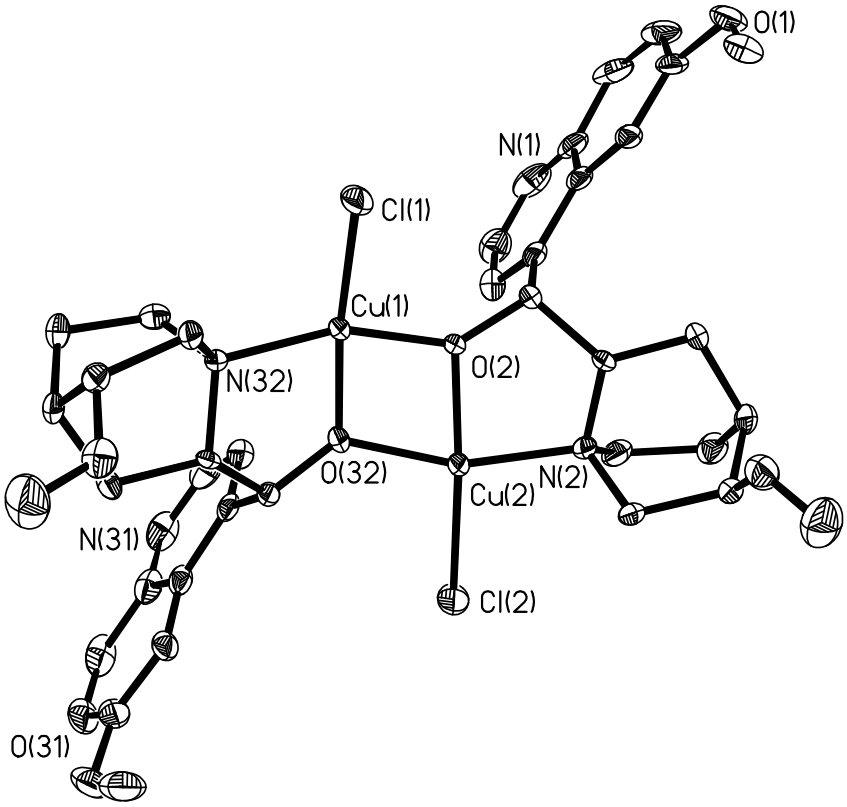


Figure 2.31: A perspective view of the asymmetric unit of complex 15. Hydrogen atoms and solvent molecules have been omitted for clarity. Selected bond lengths (Å) and angles (°): Cu(1)-Cl(1) 2.2017(14), Cu(1)-O(2) 1.921(3), Cu(1)-O(32) 1.915(3), Cu(1)-N(32) 2.003(3), Cu(2)-Cl(2) 2.1956(15), Cu(2)-O(2) 1.902(3), Cu(2)-O(32) 1.925(3), Cu(2)-N(2) 2.006(3), Cl(1)-Cu(1)-O(2) 98.82(9), Cl(1)-Cu(1)-O(32) 172.73(9), Cl(1)-Cu(1)-N(32) 100.83(10), O(2)-Cu(1)-O(32) 75.64(11), O(2)-Cu(1)-N(32) 158.83(12), O(32)-Cu(1)-N(32) 84.09(12), Cl(2)-Cu(2)-O(2) 175.02(10), Cl(2)-Cu(2)-O(32) 100.15(9), Cl(2)-Cu(2)-N(2) 99.61(10), O(2)-Cu(2)-O(32) 75.85(11), O(2)-Cu(2)-N(2) 84.41(12), O(32)-Cu(2)-N(2) 160.24(12).

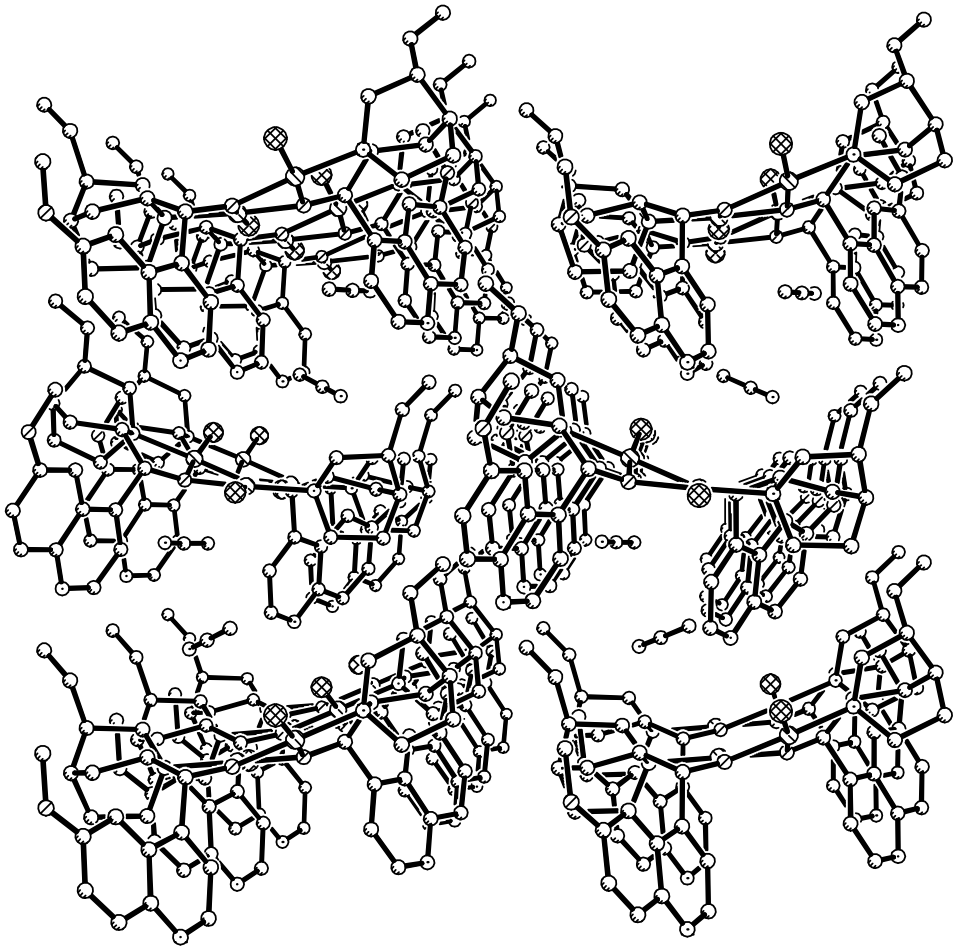


Figure 2.32: A packing diagram looking down the *x*-axis showing the acetonitrile molecules in the voids between adjacent stacks of the complex.

2-fold axis, and so the complex does not crystallize in a higher symmetry space. There are no notable intermolecular interactions between adjacent molecules; the acetonitrile molecules sit in channels between the quinoline parts of the ligand and adjacent molecules (see Figure 2.32).

Structure of 16

Complex **16** was synthesized and crystallized in the same manner as complex **15**. Upon determination of the unit cell it was observed that **16** had almost identical parameters to **15** (see Table 2.3). This observation, in conjunction with the elemental analysis, which confirmed the stoichiometry as identical to that of

Complex	*a* (Å)	*b* (Å)	*c* (Å)	*β* (°)	V (Å^3)
15	10.490(4)	15.167(6)	13.510(5)	99.477(5)	2120.1(14)
16	10.5(3)	15.2(2)	13.5(3)	99.5(9)	2120(120)

Table 2.3: A comparison of unit cell parameters for complexes 15 and 16. Although there is high error on the parameters for 16 (due to the limited amount of data used for cell determination), the parameters are remarkably similar.

15 lead to the assumption that **16** would have an almost identical structure to **15**, and so full X-ray determination was not carried out.

Structure of 17

Complex **17** crystallizes in the tetragonal space group $P4_1$, with two molecules in the asymmetric unit. Although the two molecules are related by a pseudo rotation axis, the inclusion of a molecule of methanol and one of water break the symmetry, resulting in the reported space group. Both cobalt centres have

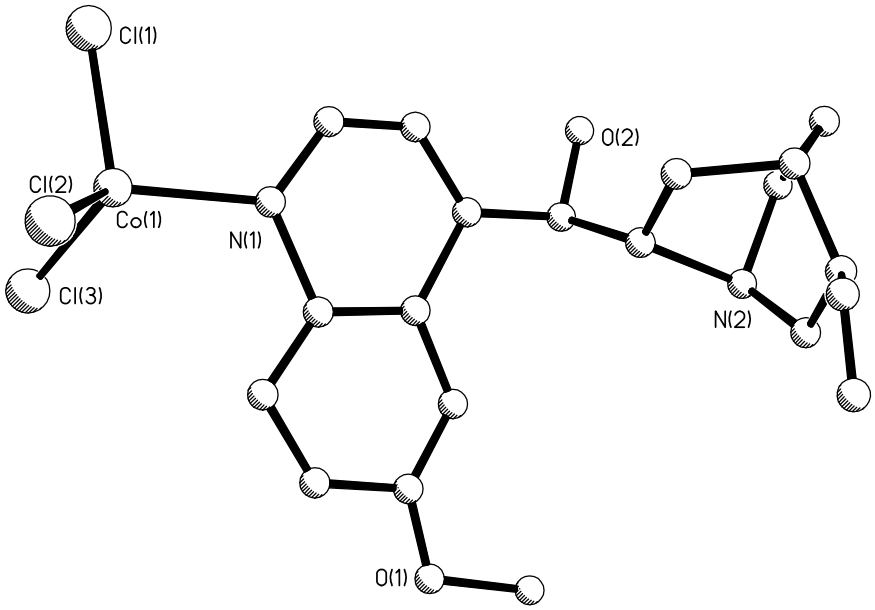


Figure 2.33: A perspective view of one molecule of complex 17. Hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): Co(1)-Cl(1) 2.265(8), Co(1)-Cl(2) 2.228(8), Co(1)-Cl(3) 2.319(8), Co(1)-N(1) 2.06(2), Cl(1)-Co(1)-Cl(2) 116.5(3), Cl(1)-Co(1)-Cl(3) 106.5(3), Cl(1)-Co(1)-N(1) 100.7(7), Cl(2)-Co(1)-Cl(3) 107.5(3), Cl(2)-Co(1)-N(1) 111.0(6), Cl(3)-Co(1)-N(1) 114.9(6).

tetrahedral geometries, and are coordinated to three chloride ligands and the quinoline nitrogen of a quinine molecule (see Figure 2.33), with angles ranging from 101.7(7) to 117.8(3)°. Observation that the crystals were pink, indicating divalent cobalt centres, led to the charge balance being accounted for by protonation of the quinuclidine nitrogen of each quinine. This type of complex has previously been synthesized by Oleksyn and co-workers,[30] although all previous complexes were crystallized in lower symmetry space groups. As the complex has no new features when compared with the previous work, and with poor quality crystals (R_{int} of 81.8%), the decision was made not to fully refine this structure.

2.4 Summary

This chapter has described the coordination and metallosupramolecular chemistry of the alkaloids nicotine and quinine. These chiral heterocyclic compounds have been used directly, without synthetic modification, to coordinate to transition metals salts to form a number of complexes. The majority of these complexes were examined by X-ray crystallography, as well as other standard experimental techniques.

The reaction of nicotine with transition metals thiocyanates resulted in the synthesis of a number of related coordination compounds. A common structural motif ran through these complexes, and could be seen in the structure of the complexes themselves, as well as the network formed by hydrogen bonds between different complexes. Comparison of the conformation of the nicotine molecule confirmed the previous computational work, with a perpendicular relationship between the two rings of the nicotine molecule.

Reaction of nicotine with silver(I) salts resulted in three different complexes. In all cases nicotine acts as a bridging ligand, and in one case also as a monodentate ligand coordinated via the pyridine nitrogen. Due to the difference between the two donor sites on the nicotine molecule, this bridging bidentate ligand aligns itself in a regular fashion in the formation of these polymeric products. This leads to the chiral coordination polymers which are directional. Amongst these complexes the conformation of the nicotine molecules is very similar to that in the previously described complexes, and again compares favorably with the earlier computational work.

A smaller number of coordination complexes of quinine were synthesized than of nicotine. Coordination of quinine was observed via three of the possible four binding domains within the different complexes.

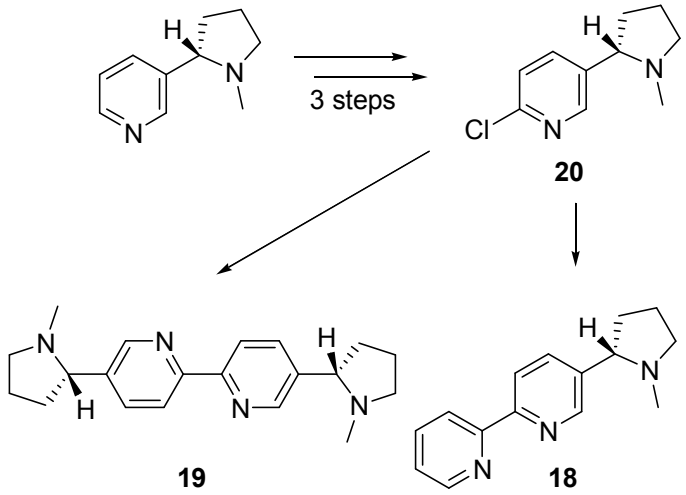
Alkaloid Organic Chemistry

3.1 Introduction

This chapter focuses on the attempted synthesis of potential ligands, using nicotine and the cinchona alkaloids as starting materials. These alkaloids are readily available as single enantiomers, which makes them attractive building blocks for the synthesis of chiral ligands. Total synthesis of nicotine- and cinchona alkaloid-based molecules which involve stereoselective synthesis of the chiral centre(s) is not covered in this thesis.

3.1.1 Nicotine

The organic chemistry of nicotine has been surprisingly unexplored. Only one paper has investigated the synthesis of nicotine derivatives as potential chiral coordination ligands. Schmidt and Neitemeier[44] reported the synthesis of 6-(2'-pyridyl)nicotine (**18**) and bis-6,6'-nicotine (**19**), via the synthesis of 6-chloronicotine (**20**) (see Scheme 3.1). 6-Chloronicotine was a key intermediate targeted in the synthesis of other new substituted nicotine derivatives.



Scheme 3.1

There has been sparse research over the last century into the derivatisation of nicotine for a variety of aims. As early as 1924 Chichibabin was investigating the amination of nicotine, employing the method named for him.[45] Another area

which has been investigated is the direct alkylation of nicotine by various methods.[46] A wide range of modifications of nicotine were investigated by Acheson, Ferris and Sinclair,[47] unfortunately few of these had any potential use in the synthesis of new ligands for coordination chemistry. There has been more recent interest in the synthesis of nicotine derivatives and analogues due to their pharmacological applications.[48-50]

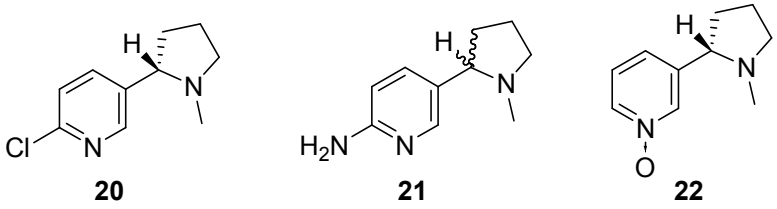
3.1.2 Quinine and the Cinchona Alkaloids

Quinine and the cinchona alkaloids have been more extensively investigated as the basis for ligands for coordination chemistry, largely due to their use in the Sharpless Dihydroxylation catalysts.[11] The organic chemistry of this family of compounds has also been more widely investigated due to the use of quinine for the treatment and prevention of malaria. A recent review by Hoffman and Frackenpohl[51] covers the majority of work in this area, as well as detailing some of the chemical history of the cinchona alkaloids.

3.2 Nicotine Chemistry

3.2.1 Introduction

Initial efforts in this area focused around the synthesis of 6-chloronicotine (**20**), as an intermediate towards the synthesis of ligands with a greater number of donor sites. Prior to this thesis **20** had been synthesized a number of times. A synthesis was reported in 1996 by Damaj and co-workers;[52] their synthesis is via 6-aminonicotine (**21**), synthesized by a Chichibabin method[45] (see Figure 3.1). Unfortunately this method racemizes the nicotine molecule, resulting in a mixture of (*S*)- and (*R*)-6-aminonicotine, and so is not useful in the synthesis of homochiral ligands. A more recent paper by Roduit, Wellig and Kiener[53] details the functionalisation of nicotine via microbial action. Unfortunately this method was unavailable. The most recent synthesis of **20** prior to the beginning of this thesis was the work of Schmidt and Neitemeier,[44] which involved the synthesis of nicotine-N1-oxide (**22**), and subsequent chlorination. This method was the one initially explored towards the synthesis of **20** and derivatives.



20 **21** **22**

Figure 3.1: From left to right: (*S*)-6-chloronicotine (20), 6-aminonicotine (21), and (*S*)-nicotine-N1-oxide (22).

Following the commencement of this thesis a number of other syntheses of nicotine derivatives appeared in the literature. The synthesis of **20** via reaction of **22** with a trialkyl amine in the presence of an electrophile to produce a cationic radical, which could subsequently be reacted with a nucleophile to produce a 6-substituted nicotine derivative, was detailed by Johansson and Svensson[49] in a patent application. This method was also attempted in this thesis and is detailed below. More recently (after this area of research had largely been abandoned) in

the work of Comins and co-workers[50], a more attractive synthesis of **20** appeared, which detailed the use of *n*-butyllithium and lithium dimethylaminoethanoate, followed by reaction with hexachloroethane.

The desire for the synthesis of **20** relates to the ease of synthesis of derivatives from such a precursor. Previous work in this group had involved the synthesis of ligands with chelating donor pockets, an increased number of binding pockets, as well as a combination of these two methods. It was intended to mimic this prior work and synthesize a series of chiral ligands (see Figure 3.2).

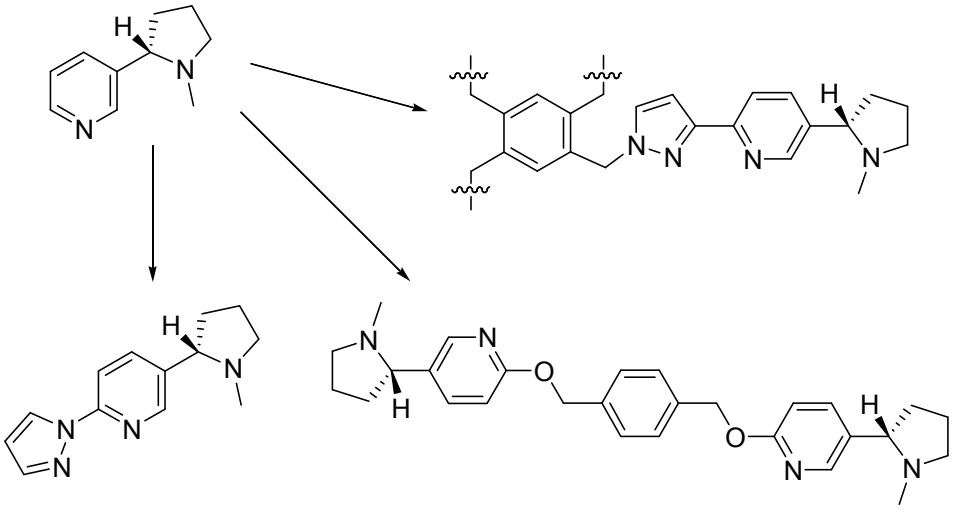
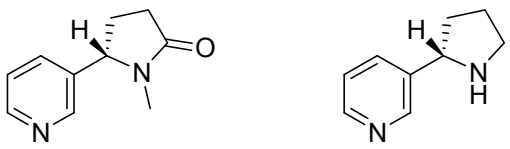


Figure 3.2: Examples of ligands that could be synthesized from nicotine, counter-clockwise: a ligand with a chelating donor site, a ligand with bridging donor sites, a ligand with multiple chelating donor sites (only one arm shown).

Although the synthesis of **20** was the primary starting target for the synthesis of nicotine based ligands, a number of other synthetic routes to derivatives of nicotine were explored. Synthesis of cotinine (**23** – see Figure 3.3) was one route investigated. This molecule had previously been synthesized[54], and was also



23 **24**

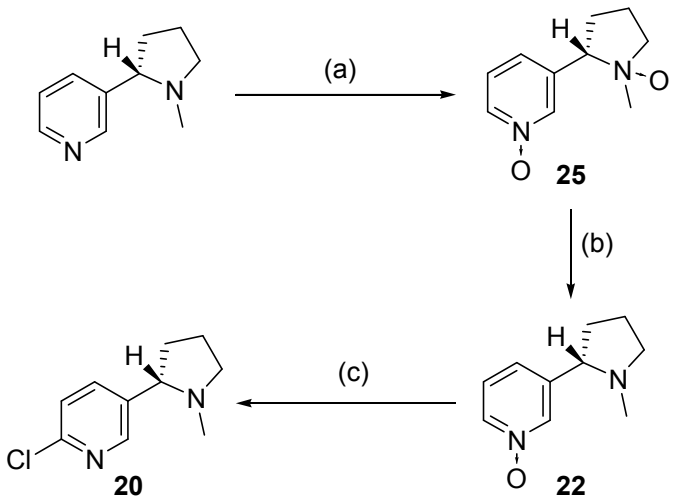
Figure 3.3: Cotinine (23) and nornicotine (24).

known as a metabolite of nicotine produced in the human body. Synthesis of nornicotine (**24** – see Figure 3.3), another known metabolite of nicotine, was also attempted, as potential precursor to new nicotine based ligands.

3.2.2 Synthesis of 6-Chloronicotine and Related Reactions

A variety of methods were attempted for the synthesis of 6-chloronicotine (**20**). Initially, known methods were focused on, and later alternative syntheses were attempted.

The first method attempted in the synthesis of **20** was that of Schmidt and Neitemeier[44] (see Scheme 3.2). The initial step in this process is the synthesis of nicotine-di-N-oxide (**25**) via literature procedures.[55] This synthesis was carried out without problems, and provided the desired product in high yield. The next step was chemoselective reduction to the pyridine mono-N-oxide (**22**). In the original synthesis by Taylor and Boyer[55] this was done by reaction of the **22** with gaseous sulfur dioxide bubbled through water. Schmidt and Neitemeier adjusted this method, using a mixture of 40% aqueous sodium bisulphite solution, acetic acid and water. The original method was attempted, and was successful, albeit

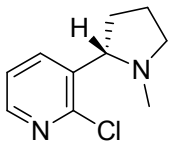


(a) CH_3COOH, H_2O, H_2O_2; (b) $SO_2(g)$, H_2O or $NaHSO_3$, H_2O, CH_3COOH; (c) $POCl_3$, $((iPr)_2NH)$, CH_2Cl_2

Scheme 3.2

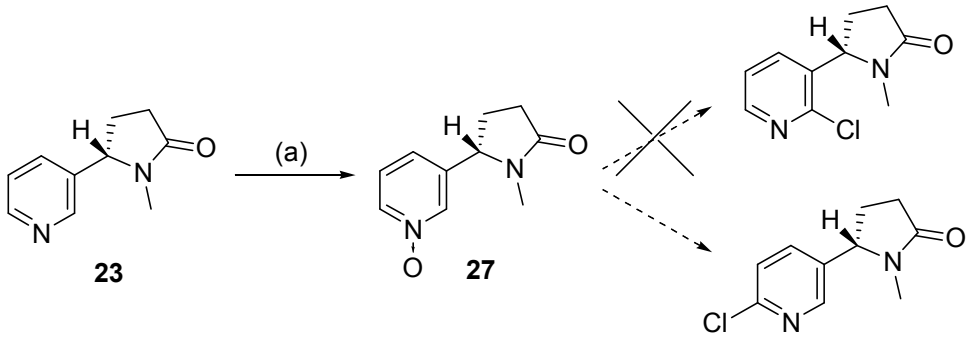
with a low yield. This method had to be abandoned due to a lack of access to gaseous sulfur dioxide in sufficient quantities. The method utilized by Schmidt and Neitemeier was also attempted, and met with mixed success, with yields ranging from low (10%) to moderate (60%) in small scale reactions (~100mg scale). Attempts to upscale this reaction invariably led to yields at the low end of the scale (10-20%), and isolation via column chromatography was less successful than that of Schmidt and Neitemeier in this case. Synthesis of **20** by the method of Schmidt and Neitemeier was then attempted, but unfortunately did not yield any of the desired products. This reaction was attempted both in the presence and absence of diisopropyl amine (as detailed in the original paper), but neither method was successful despite repeated attempts.

Following on from the above work was the synthesis of cotinine (**23**) as an intermediate in the synthesis of a substituted nicotine derivative. This was attractive for a number of reasons; in contrast to the amine subunit of nicotine the amide of **23** cannot be N-oxidized, resulting in a one step synthesis of the pyridine-N-oxide (**27**), as no reduction is required. There is a further advantage in the chlorination step; Schmidt and Neitemeier in their work noted the synthesis of both 2-chloronicotine (**26** – see Scheme 3.3) and **20** when reacting **22** with phosphorus oxychloride. They attributed the chlorination of the more sterically hindered 2-position to interaction between the amine nitrogen and the phosphorus species placing the chlorine in the closer position. Addition of diisopropyl amine to compete with the substrate for this interaction suppressed this pathway, resulting in only the formation of **20**. In the case of cotinine, it was thought that the amide would not interact with the phosphorus species in the same way, so only substitution at the less hindered 6-position would occur (see Scheme 3.4).



26

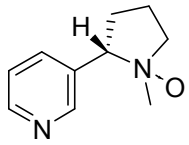
Scheme 3.3



(a) H_2O_2, CH_3COOH

Scheme 3.4

The synthesis of **23** was performed by literature methods[54], then N-oxidized by adapting the procedure for the synthesis of **25**. Cotinine was reacted with hydrogen peroxide in acetic acid to provide cotinine-N-oxide (**27**) in excellent yield (99%). Compound **27** was then reacted with refluxing phosphorus oxychloride. Following workup, NMR spectroscopy revealed some interesting features; the aromatic region remained the same as in the starting material, with four peaks being visible, while the spectrum for the five-membered ring was significantly different. This indicated that the five-membered ring was unstable to reaction with phosphorus oxychloride, and had possibly undergone ring-opening. Following this result, **23** was also reacted with phosphorus oxychloride. Analysis by NMR revealed that in this case also, the five-membered ring had undergone some sort of reaction, possibly ring-opening. A further probe of the reactivity of the N-oxides was the reaction of **25** with phosphorus oxychloride. After removal of the reagent by vacuum distillation, and neutralisation of the residue, no products could be extracted, indicating either complete destruction or polymerization of the starting material. To test whether this was due to the presence of the amine-N-oxide, or both, nicotine-N'8-oxide (**28** – see Scheme 3.5) was synthesized by the method of Taylor.[55] Compound **28** was reacted with phosphorus oxychloride at reflux, which was subsequently removed by vacuum distillation. No products could be extracted from the residue, again indicating either complete destruction or polymerization of the starting material.

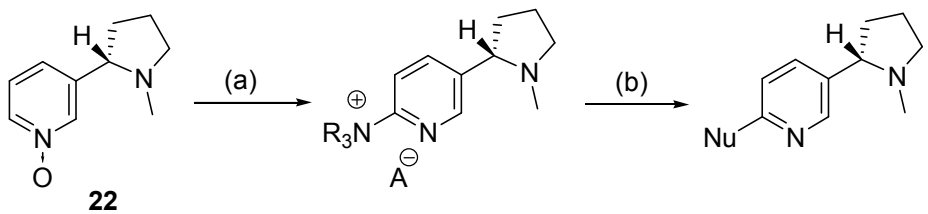


28

Scheme 3.5

Another series of reactions was the attempted acylation of the N-oxides by acetic anhydride at elevated temperatures.[56] This reaction was attempted with all three N-oxides (**22**, **27** and **28**) as well as **23**. After workup a variety of results were observed. Nicotine N-oxides **22** and **28** displayed no reaction, with only the starting material observed by NMR. The reactions of **23** and **27** were both unsuccessful as well, although in these cases analysis by NMR showed similar spectra to those from the reaction of these compounds with phosphorus oxychloride, possibly indicating some sort of ring opening of the five-membered ring.

Another route to 6-substituted nicotine derivatives investigated was through the work of Johansson and Svensson.[49] This involves the reaction of nicotine-N1-oxide with a trialkylamine in the presence of an electrophilic compound to produce 6-substituted nicotine species, which can be readily substituted by nucleophiles to produce the desired nicotine derivative (see Scheme 3.6). The original method reported the use of dry gaseous trimethylamine in the reaction. This was unavailable, and so triethylamine was used in its place. Unfortunately, after workup, analysis by NMR showed none of the desired product. The original report claims the use of multiple trialkyl and triaryl amines, but only gives details for the use of trimethylamine, and so cannot be completely relied upon.

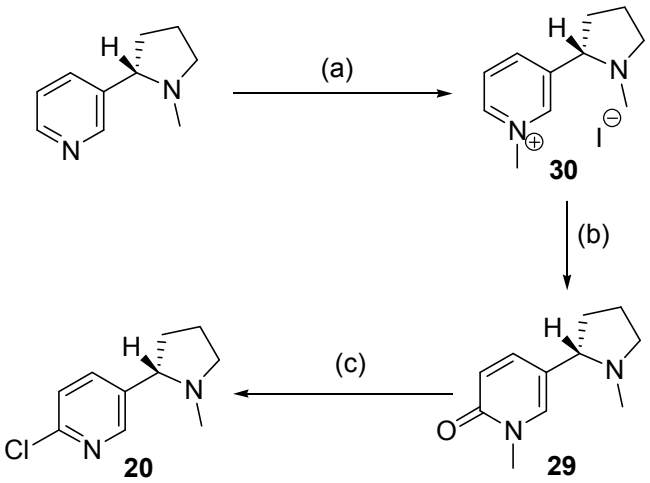


22

(a) NR_3, AX (b) Nu

Scheme 3.6

An alternative method pursued towards the synthesis of **20** was via N1-methylnicotin-6-one (**29**). Synthesis of **29** was achieved by the method of Acheson, Ferris and Sinclair,[47] involving initial synthesis on N1-methyl nicotinium iodide (**30**), followed by oxidation with basic ferricyanide (see Scheme 3.7). Reaction of **29** with refluxing phosphorus oxychloride resulted in **20** in varying yields. On a small scale (~30mg) this reaction would proceed in 30-60% yield, which appeared to be related to the solubility of **29** in the solvent. On a larger scale the yield of **20** decreased, to 5-10%, and significant amounts of the starting material were observed. It was observed that most of the starting material was not dissolved in the solvent (phosphorus oxychloride), and simply adhered to the walls of the reaction vessel. On a small scale, there was significant agitation possible by the magnetic stir bar, which appeared to force more of the starting material into solution. On the larger scale, such agitation was not possible, and so the yield significantly decreased.



(a) MeI, CH_3COOH; (b) $K_3Fe(CN)_6$, NaOH, H_2O
(c) $POCl_3$

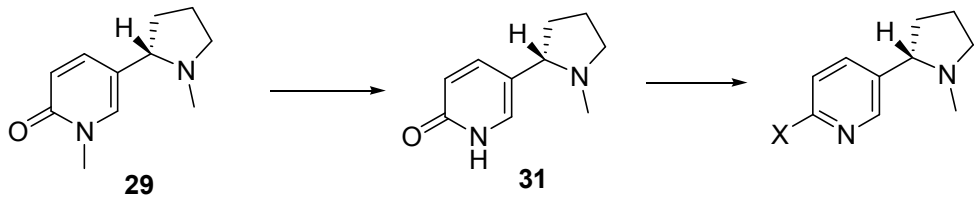
Scheme 3.7

Various attempts were made to increase the solubility of the starting material; one avenue of investigation was through the use of different solvents. As phosphorus oxychloride is highly reactive, only chlorinated solvents were used in the reactions. The first solvents trialled were chloroform and 1,2-dichloroethane; unfortunately both these solvents have lower boiling points than phosphorus oxychloride, and no reaction occurred at reflux. The next solvent trialled was 1,2-dichlorobenzene, which has a significantly higher boiling point (180 °C).

Reactions were attempted at both ~105 °C and at 180 °C. With low amounts of phosphorus oxychloride (half to one equivalents), no reaction, or only a trace of **20** was observed. As the amount of phosphorus oxychloride was increased it was noted that the solubility of **29** in the solvent decreased, and it adhered to the walls of the vessel. Unfortunately the desired **20** was still not obtained. Due to the low yields and difficulty in scaling, this method had to be abandoned for the preparation of **20**.

After the above method had been abandoned, a number of other synthetic procedures were attempted with **29** to try and access nicotine derivatives that would be useful synthetically.

The first pathway investigated was the demethylation of **29** in an attempt to synthesize nicotin-6-one (**31** – see Scheme 3.8), which is tautomeric with 6-hydroxynicotine. This type of pyridone is much more readily substituted than N-alkyl derivatives. A number of methods were attempted for this transformation. Catalytic hydrogenation, using palladium on carbon in dry dichloromethane was attempted; after workup the NMR showed only starting material. This was repeated using Pearlman's Catalyst (palladium hydroxide on carbon) as the catalyst; unfortunately again, NMR showed only starting material after workup. Boron tribromide, a well known demethylation/dealkylation agent was used; again, after workup only starting material was observed by NMR.

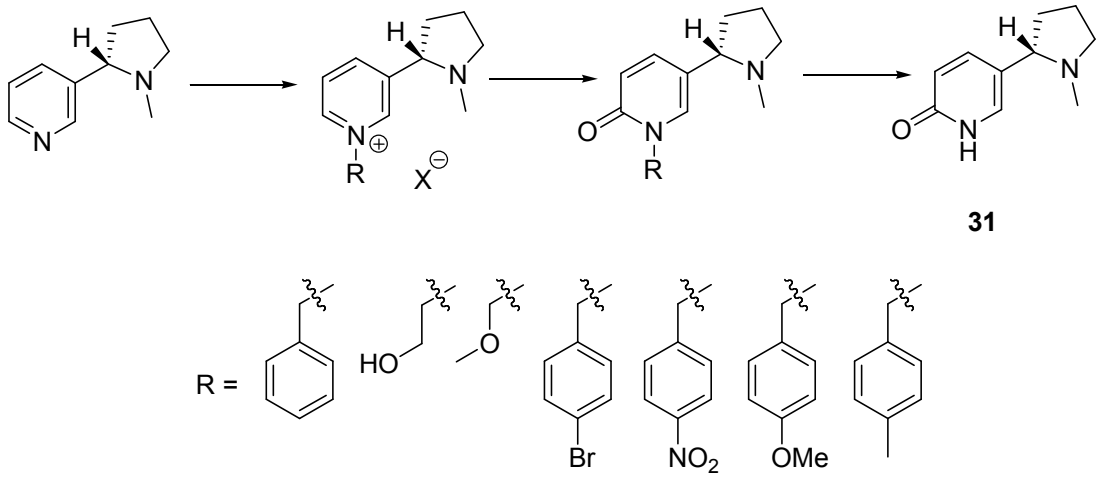


Scheme 3.8

The other synthetic pathway explored was the attempted synthesis of 6-bromonicotine (**32**) from **29**. A number of methods were explored in the attempted synthesis of **32** from **29**. The first method tried was simply the reaction of **29** with phosphorus tribromide. Initially this reaction was tried in dry

chloroform, and after workup NMR showed no product present. The reaction was repeated in neat phosphorus tribromide; unfortunately this was also unsuccessful with only the starting material observed by NMR following workup. The second method attempted followed the work of Kato and co-workers,[57] which recognizes the mechanism of reactions of phosphorus oxytrihalides. This mechanism involves reaction of the phosphorus species with the N-substituent, activating the 2-position towards substitution; subsequent reaction by a halide present in solution results in the desired product being formed. Recognising this mechanism, Kato proposed to substitute phosphorus oxyhalide with a mixture of phosphorus pentoxide and a tetraalkylammonium halide. Reaction of **29** under these conditions, followed by workup, unfortunately showed only the starting material present by NMR. The final method attempted was from the work of Sugimoto, Mori and Tanji,[58] and was originally intended as a method of synthesis via **31**. Reaction of **29** with N-bromosuccinimide and triphenylphosphine in dioxane, followed by workup, showed only the starting material present by NMR.

Following on from the unsuccessful synthesis of 6-halonicotines from N-methylnicotine-6-pyridone, either by direct halogenation, or by demethylation then halogenation, another route was investigated. This involved the preparation of other N-substituted nicotin-6-one derivatives, with an aim to access **31**. A range of N-substituents were investigated (see Scheme 3.9).



Scheme 3.9

The first substituent investigated was a simple benzyl group. N-Benzylnicotinium bromide (**33**) was synthesized by the reaction of nicotine with benzyl bromide in acetic acid, in moderate yield (42%). Reaction of **33** with basic ferricyanide provided the desired N-benzylnicotine-6-pyridone (**34**) in moderate yield (60%). Although this compound was intended for debenzylation in the synthesis of **31**, a number of other reactions were attempted on it.

Chlorination of **34** was attempted by the method used for the chlorination of **29**, namely reaction of **34** with refluxing phosphorus oxychloride. Following workup, analysis of the products by NMR revealed only the starting material. The bromination reactions attempted on **29** were also trialled on **34** (see above for details). Unfortunately all three of these methods failed, returning only starting material.

The debenzylation of **34** was attempted by a number of different methods. Initially reaction with boron tribromide was attempted; following workup only starting material was observed by NMR. Catalytic hydrogenation was also attempted by a number of related methods. Compound **34** was stirred in acetic acid with palladium on carbon as a catalyst under a hydrogen atmosphere. Following workup only the starting material was observed by NMR. Repetition of this method with Pearlman's Catalyst in place of palladium on carbon, with trifluoroacetic acid in place of acetic acid, and both these adjustments at the same time were all performed; in all cases analysis by NMR following workup revealed only the starting material.

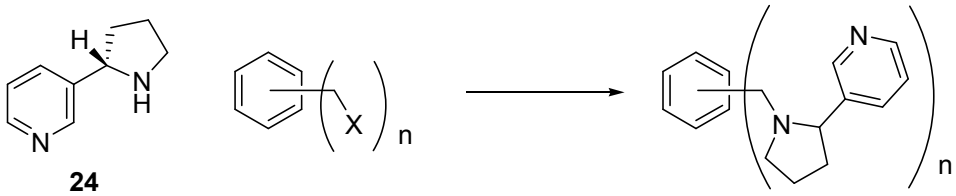
Following the failed debenzylation of **34** the synthesis of a number of other N-substituted nicotine derivatives was attempted. Reaction of nicotine with 2-bromoethanol failed to produce an N-substituted derivative. Reaction with chloromethyl methyl ether also failed to produce an N-substituted derivative. Reaction with both 1-bromomethyl-4-nitrobenzene and 1-bromomethyl-4-bromobenzene resulted in the desired respective nicotinium species **35** and **36**. When the syntheses of the respective pyridone species **37** and **38** were attempted, the nicotinium species were insoluble in the reaction mixture. Attempts to solubilize the starting materials by changing from an aqueous

system to a mixture of water and methanol did not alleviate this problem; if the mixture was adjusted sufficiently for the dissolution of the nicotinium species, invariably the iron species precipitated out of solution. Reaction of nicotine with both 1-chloromethyl-4-methoxybenzene and 1-bromomethyl-4-methylbenzene resulted in the desired nicotinium species **39** and **40**. Synthesis of the respective pyridone species, **41** and **42**, was attempted, and again the nicotinium species were insoluble in the reaction mixture. For these two reactions, dissolution of the nicotinium species while maintaining the solubility of the iron(III) cations was achieved. Following workup NMR analysis of the products in both cases revealed nicotine; the nicotinium species were not robust enough to withstand the high pH in the reaction mixture, and had hydrolysed back to nicotine.

3.2.3 Other Reactions of Nicotine

A number of other approaches were investigated towards the synthesis of nicotine derivatives as potential ligands for use in coordination and metallosupramolecular chemistry. These approaches are reported below.

The demethylation of nicotine to **24** was one approach investigated. Compound **24**, although a potential ligand itself, is attractive because it could be readily substituted onto the type of cores that have been extensively studied by this group,[59] to prepare a range of related ligands with differing numbers and arrangements of donor groups (see Scheme 3.10). Previous work on the preparation has focussed on a number of different ways of preparing **24**: most recent work has reported the stereoselective synthesis of **24** from other chiral starting materials or in the presence of chiral auxiliaries.[60] Prior to this many syntheses relied on resolution of a mixture of both enantiomers of **24** (or of



24

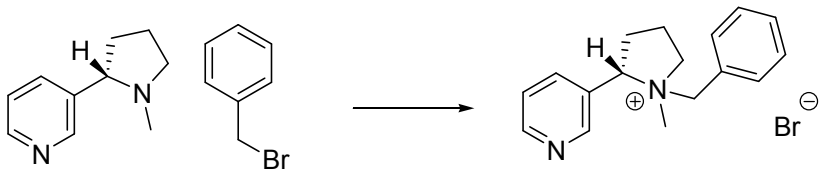
Scheme 3.10

diastereomeric salts),[61] while the least explored method is the synthesis directly from nicotine by demethylation.[62, 63] The syntheses directly from nicotine were either too low yielding to be of synthetic use,[62] or were by methods unavailable to us.[63] In this thesis the direct demethylation of nicotine was investigated, with four different methods being investigated. Reaction of nicotine with boron tribromide returned only starting material, as did reaction with refluxing trifluoroacetic acid. Catalytic hydrogenation of nicotine in acetic acid with either palladium on carbon, or Pearlman's Catalyst also returned only starting material.

Another route to 6-substituted nicotine derivatives was the synthesis of **21**, a known reaction originally reported by Chichibabin.[45] This reaction was successfully performed, and the 2- and 6-aminonicotine were separated by column chromatography. Shortly thereafter, a more complete translation of the original paper was obtained, which revealed that this synthetic method resulted in racemisation of the nicotine molecule. As the aim of this thesis was the synthesis of homochiral ligands, this approach was then abandoned.

The reaction of nicotine with alkyl halides had been explored earlier, when attempting to synthesize **20**. These reactions were performed in acetic acid, and it can be assumed that initially both nitrogen atoms are protonated. The amine nitrogen in these cases is too strongly basic to be deprotonated, and so alkylation only occurs at the pyridine nitrogen. Another avenue of exploration would be the linking two or more molecules of nicotine together with an alkyl linker to create a cationic ligand with multiple donor sites. Ideally the amine nitrogens would be linked together, as the pyridine nitrogen atom of nicotine is the preferred donor. Investigation of the literature revealed the work of Yoshizawa and co-workers,[64] where nicotine is reacted with benzyl bromide in

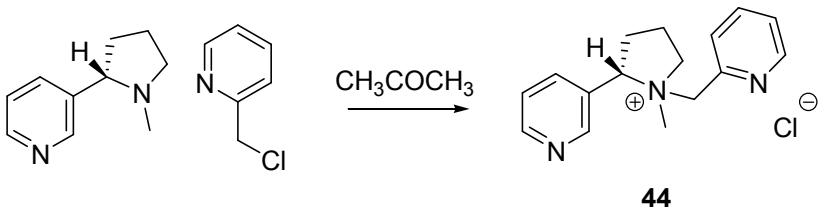
acetone, synthesising N'8-benzyl nicotinium bromide (**43** – see Scheme 3.11). This reaction was successfully repeated, and then attempts were made to adapt it to other alkyl halides. The reaction of nicotine with 1,4-bisbromomethylbenzene was the first investigated; reaction in acetone followed by workup provided a brown tar-like product. Analysis by NMR in deuterium oxide revealed that several species were present in the product mixture. The reaction of alkyl halides with the amine nitrogen of nicotine locks the position of the methyl group of the pyrrolidine ring; prior to reaction the molecule can equilibrate between two possible orientations. After substitution a new stereocentre is formed. The large number of peaks observed indicated that both chiralities were being formed in the reaction; as more than one nicotine molecule was being attached to the alkyl linker, there was a large possible mix of diastereomeric molecules present. There are three possible combinations of stereocentres possible: (*S*,*S*,*S*,*S*), (*S,R,S,S)* and (*S,R,R,S*). This does not account for the larger number of peaks observed in the spectra, and so it was postulated that in this case the pyridine nitrogen was also reacting, adding further possible products that could be observed. Separation was not attempted as there was no major product, and the mixture was only soluble in strongly polar solvents. The reaction with both the 1,2- and 1,3-bisbromomethylbenzenes was also explored, and had the same result, with multiple products being formed.



43

Scheme 3.11

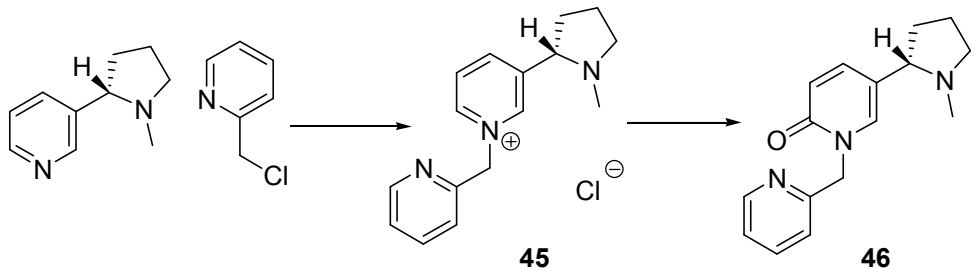
An adjustment to this proposal was reacting nicotine with picolyl chloride, attempting to synthesize N'8-picolylnicotinium chloride (**44** – see Scheme 3.12), a potential bridging ligand. Although the reaction with bisbromomethylbenzenes had failed, it was hoped that the smaller molecule, similar to benzyl bromide would not encounter such problems. Unfortunately this was not the case, and after workup analysis by NMR revealed multiple products present. It appeared in



Scheme 3.12

this case that there were more than three products, indicating that substitution onto attached picolyl nitrogens may have been occurring.

After the attempted synthesis of **44** failed, a variation of this theme was investigated. As the synthesis of pyridine-N-substituted nicotines molecules could be carried out successfully, it was decided to attempt the synthesis of N1-picolylnicotinium chloride (**45** – see Scheme 3.13), which could subsequently be oxidized by basic ferricyanide to N1-picolylnicotine-6-pyridone (**46**). Compound **46** could potentially chelate a metal centre by coordination of picolyl nitrogen and the pyridone oxygen, while still having the amine nitrogen available for further coordination. Compound **45** was successfully synthesized by the reaction of nicotine with picolyl chloride in acetic acid in a yield of 94%. Oxidation by basic ferricyanide resulted in compound **46** in a yield of 57%.



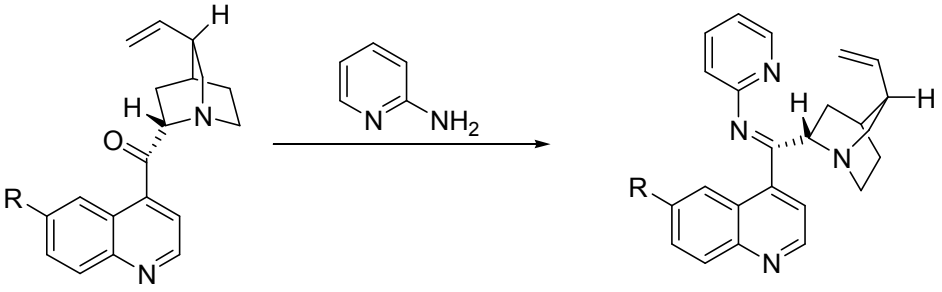
Scheme 3.13

3.3 Cinchona Alkaloid Chemistry

3.3.1 Introduction

A range of different chemistry was investigated in this area, focusing around the derivatisation of the cinchona alkaloids at the C9 position.

The synthesis of quininone (**47**) or cinchonidinone (**48**) was the target as an intermediate on the route to the preparation of potential ligands. An example of the type of chemistry that would be attempted is the reaction of one of these ketones with 2-aminopyridine to synthesize **49** (see Scheme 3.14). This molecule would have a bi- or possibly tri-dentate binding pocket, as well as additional coordination sites at the quinoline nitrogen and vinyl group. These factors would make ligands of this type ideal for the synthesis of chiral coordination polymers and/or mixed-metal complexes. There is a wide range of amines available, which would lead to a wide range of potential ligands.



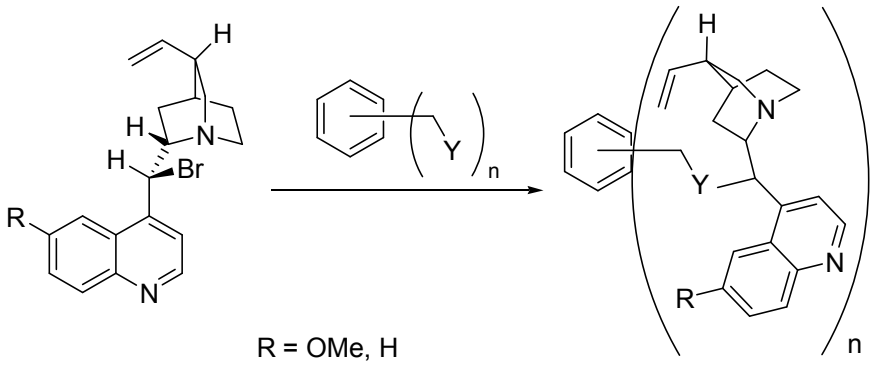
R = OMe : **47**
R = H : **48**

49

Scheme 3.14

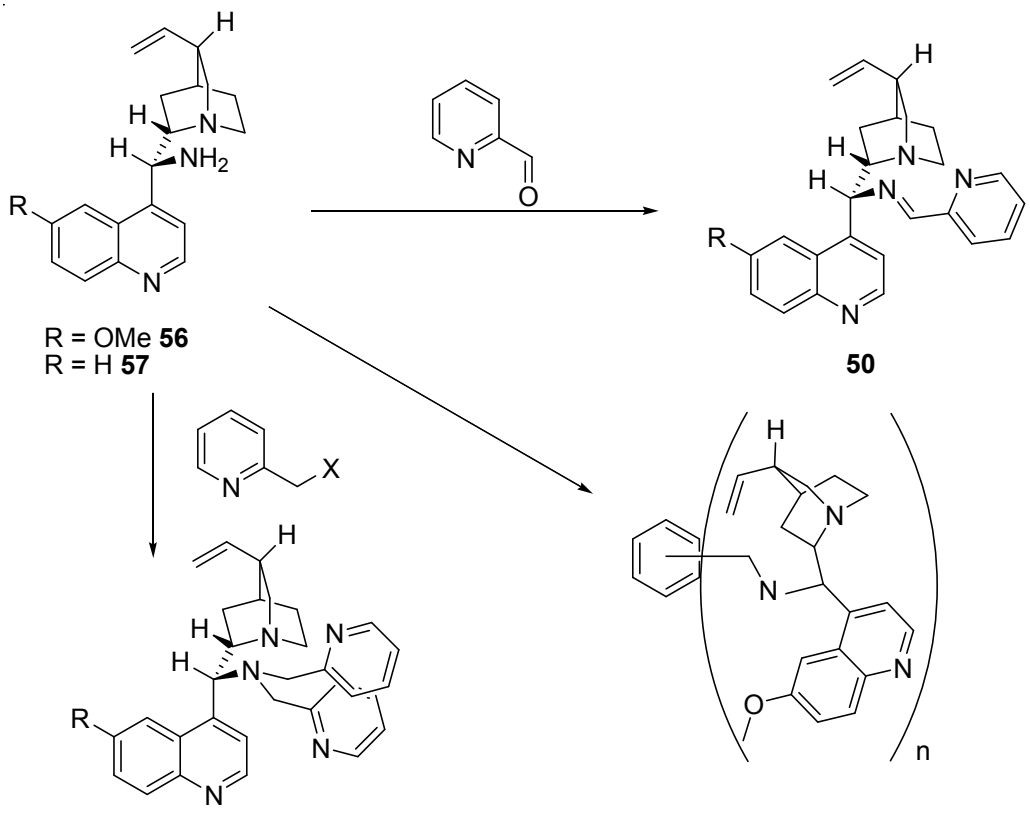
Bromination of cinchona alkaloids at the C9 position was also explored. These derivatives would be readily substituted onto the range of multi-armed heterocyclic cores previously utilized in this group (see Scheme 3.15).[59]

The final route investigated in this area was the synthesis of 9-amino-(9-deoxy)*epi*-cinchona alkaloids. These molecules, potentially ligands themselves,



Scheme 3.15

could be readily substituted in a number of ways to produce derivatives with greater numbers of donor sites and/or greater denticity. One example, complementary to **49**, is the reaction of a 9-amino-(9-deoxy)*epi*-cinchona alkaloid with pyridine-2-carboxyaldehyde (see Scheme 3.16). This would result in a potential ligand (**50**) with similar properties to **49** and would be interesting for comparison. Other avenues for derivatisation of these amines reaction with



Scheme 3.16

pyridine-methyl halides, to add further donor sites, or with poly-bromomethyl benzenes to link multiple amine moieties together.

3.3.2 Cinchona Alkaloid Organic Chemistry

The synthesis of cinchonidinone (**48**) from cinchonidine was investigated, as a precursor to potential new ligands. The synthesis of quininone (**47**) from quinine by Woodward, Wendler and Brutschy[65] was used as a template for the synthesis of **48**, although some details of the synthesis were adjusted (see Experimental Section). Analysis by NMR following synthesis revealed twice the number of expected signals. Crystals of the product were also obtained shortly after synthesis, and were suitable for X-ray crystallography. Compound **48** crystallizes in space group C2 with two molecules in the asymmetric unit (see Figure 3.4), which differ from each other in the conformation of the vinyl group. There are no significant long range packing effects between molecules of **48** in the crystal structure. Consideration of the NMR results indicates that two related products were formed from the reaction. When the reaction conditions for the synthesis of **48** were examined it became obvious that the synthesis has resulted in both **48** and cinchoninone (**51**). After the formation of **48**, in the reaction mixture in the presence of base, it exists in equilibrium with enolate **52**, which can convert to both **48** and **51** (see Scheme 3.17). The equilibrium results in the epimerisation of the variable stereocentre. Within the cinchona alkaloids there are only two

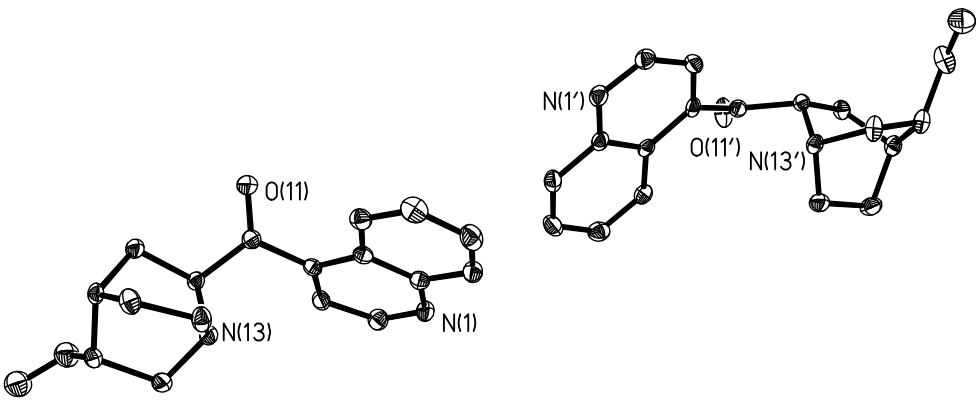
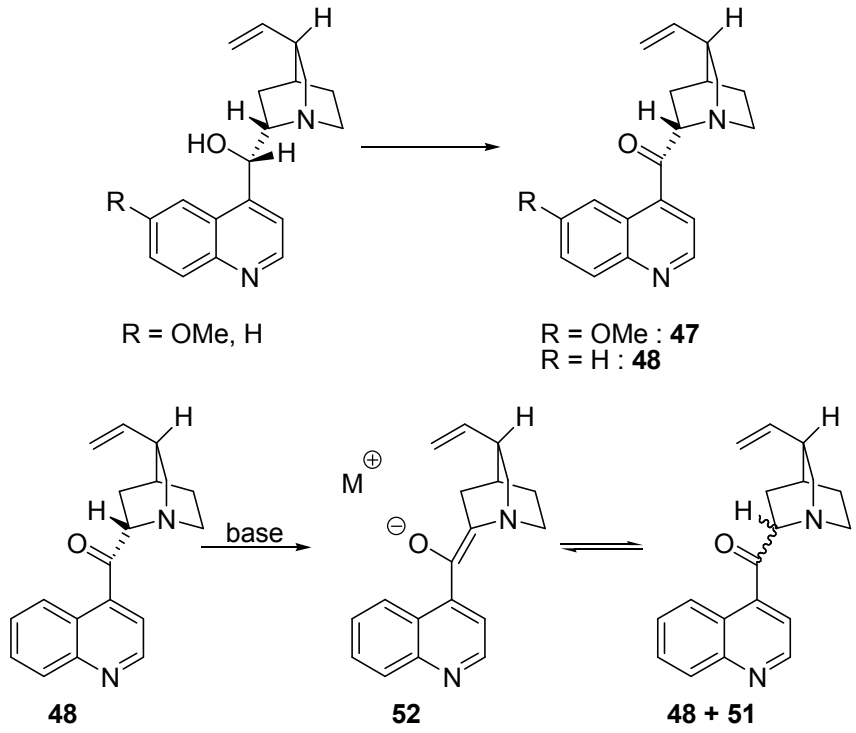


Figure 3.4: The asymmetric unit of 48 (hydrogen atoms are omitted for clarity).

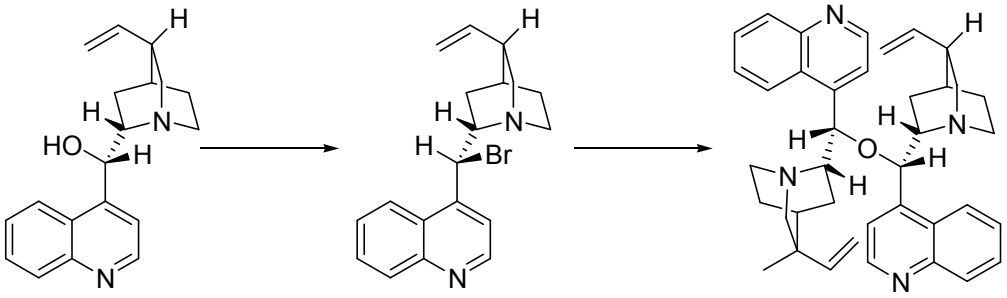


Scheme 3.17

variable stereocentres of the five that exist in the molecule (see Section 2.1.2 for further details). This ultimately means that this is not a viable route to the synthesis of homochiral ligands for coordination chemistry.

The second avenue towards synthesising new ligands from the cinchona alkaloids was based on the bromination of quinine at C9 to synthesize 9-bromo-(9-deoxy)*epi*-quinine (**53**), as reported by Hoffman and co-workers.[66] This synthesis was repeated using cinchonidine in the place of quinine to synthesize 9-bromo-(9-deoxy)*epi*-cinchonidine (**54**). Initial analysis of the product by ^{1}H NMR spectroscopy suggested that the synthesis of **54** had been successful. Analysis by mass spectroscopy however revealed the major product to have a mass of 613, significantly more that the 386 expected. Analysis by ^{13}C NMR spectroscopy revealed that the signal for C9, expected at around 30 ppm was absent, and an unexpected peak was present at 71 ppm. The unexpected peak was consistent with an ether carbon atom, and this, in conjunction with the close to doubling of the molecular weight from the starting material, led to the conclusion that two quinine molecules had been joined together. It is believed

that the reaction takes place via synthesis of **54**, and then *in situ* reaction with cinchonidine leads to the formation of **55**. The synthesis of **54** involves an inversion at C9, due to the S_N2 reaction mechanism; the reaction to form **55** is thought to proceed by re-inversion at C9 of **54** (again with an S_N2 reaction mechanism), resulting in identical stereochemistry in both halves of the molecule. This result is consistent with the NMR results, which have signals for only half the molecule – this is a result of two-fold symmetry of some kind, and as three stereocentres remain unchanged during the reaction this symmetry cannot be an inversion or mirror plane. The similarity of the NMR spectra to that of the starting material, along with consideration of the reaction mechanism, leads to assignment of the stereochemistry as **55** with C_2 symmetry (see Scheme 3.18).



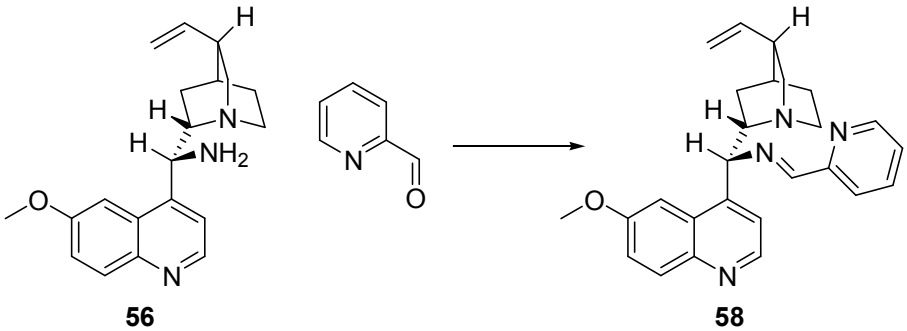
54 **55**

Scheme 3.18

The next route explored for the modification of cinchona alkaloids was the synthesis of 9-amino-(9-deoxy)*epi*-quinine (**56**). The synthesis of **56** has been previously reported by Brunner, Buegler and Nuber,[67] and was repeated. It employs a Mitsunobu reaction,[68] which directly converts a primary or secondary alcohol to an amine. Initially the reaction was repeated as reported in the original paper, but increasing the amount of hydrazoic acid approximately three and a half fold, using anhydrous solvents, and performing the reaction in an inert atmosphere increased the ratio of product:starting material from 2:1 to 10:1. The original report does not give complete details on how **56** was purified, simply stating the purification was done by column chromatography. Repeated attempts were made to remove the starting material using a variety of solvent systems, as

well as both alumina and silica columns, all resulting in loss of product and an increase in the amount of starting material. It appears that the amine either adheres permanently to the column or is unstable to column chromatography. One interesting feature of this compound is the ^{1}H NMR spectrum. In the original report the aromatic region of the spectra is reported as a multiplet spanning 0.8 ppm and a single identified peak at 8.60 ppm. When the proton NMR of the product (the 10:1 mixture) was examined, it became obvious that there were some interesting features. The broadening of the signals for H_3 and H_5 indicated that intramolecular hydrogen bonding, or some other type of NH_2-CH interaction was occurring. Synthesis of the analogous amine (**57**) from cinchonidine by this method was unsuccessful.

Although **56** could not be purified, two reactions were attempted to probe the usefulness of the unpurified material. Compound **56** was dissolved in dichloromethane and reacted with an equimolar amount of palladium dichloride bisbenzonitrile. This led to an immediate yellow precipitate that could not be filtered. The solution was reduced *in vacuo* and water added, after which the solid was removed by filtration. The melting point of this product was greater than 330 °C, which is significantly higher than the starting materials or the quinine present. The product was insoluble in all common laboratory solvents except DMSO and DMF, so analysis by NMR was performed in d_6-DMSO. The NMR spectrum appears to indicate coordination of the palladium centre to both amine nitrogens of **56**. The attempted recrystallisation by slow diffusion of various solvents into a DMF solution of the product failed to provide a pure crystalline product.

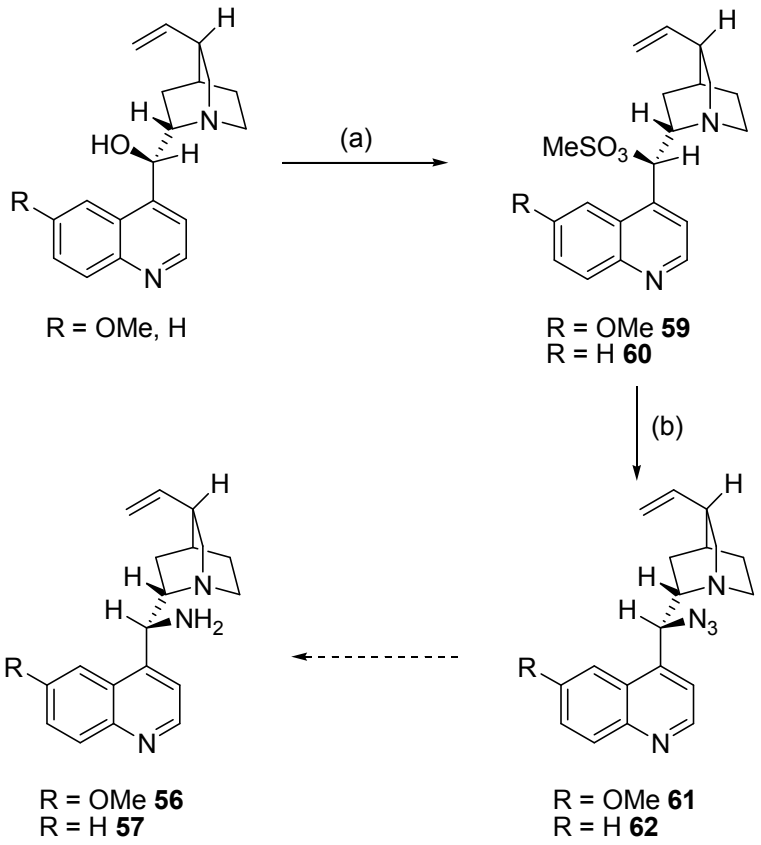


56 **58**

Scheme 3.19

The second reaction to probe the usefulness of unpurified **56** was the reaction with pyridine-2-carboxaldehyde to form imine **58** (see Scheme 3.19). Although **58** was successfully synthesized, it could not be separated from the quinine present.

After the synthesis of **56** by the method of Brunner, Beugler and Nuber[67] was abandoned, because the starting material could not be removed from the product mixture, another route to **56** (and to the analogous **57**) was investigated. Preparation of the mesylate (**59** and **60**, respectively), followed by conversion to an azide (**61** and **62**, respectively), then reduction would result in the desired amine (see Scheme 3.20). The appropriate alkaloid was reacted with methane sulphonic acid, in the presence of triethylamine in anhydrous THF under an inert atmosphere. In the case of quinine this reaction failed, and none of the desired mesylate was isolated; in the case of cinchonidine the synthesis was successful.



(a) $MeSO_3H$, Et_3N, THF
(b) NaN_3, DMF

Scheme 3.20

Unfortunately all attempts at synthesis of **62** failed, so this route was not pursued any further. It appeared that **60** was too unstable to substitution, as invariably cinchonidine was isolated from all attempts at this conversion.

3.4 Summary

This chapter reports the investigation of the organic chemistry of nicotine and the cinchona alkaloids directed towards the synthesis of new ligands for coordination and metallosupramolecular chemistry.

6-Chloronicotine (**20**) was identified as a key intermediate towards the synthesis of more substituted nicotine derivatives. A number of methods for the synthesis of **20** were investigated. Unfortunately all methods ultimately had to be abandoned due to a variety of factors. The aim of synthesising nicotine derivatives via **20** went unachieved.

Other routes towards the synthesis of nicotine derivatives were investigated. The synthesis of nornicotine (**24**) was investigated by several unsuccessful methods. The syntheses of cationic ligands by the reactions of nicotine with poly-bromomethylbenzenes, as well as picolyl chloride, were investigated. It was intended to quarternize the amine nitrogen, with the pyridine nitrogen left free to coordinate to metal centres. The synthesis of a related ligand, N-picolylnicotin-6-one (**46**) was successful.

Derivatisation of the cinchona alkaloids focused around reactions at the C9 position. Three different derivations were investigated. Synthesis of the C9-ketones had to be abandoned, as the synthesis resulted in epimerisation of the adjacent chiral centre, defeating the aim of synthesising homochiral derivatives. The synthesis of 9-amino-(9-deoxy)*epi*-quinine (**56**) was successful. Unfortunately this compound could not be purified, and was not further pursued. Finally bromination of cinchonidine was investigated, but resulted in dimerisation to form ether **55**.

Amino Acid Organic Chemistry

4.1 Introduction

The organic chemistry of amino acids has been widely studied. As such amino acids are an obvious choice for incorporation into ligands for coordination and metallosupramolecular chemistry. One area where amino acids have been extensively utilized for this purpose is the synthesis of amino alcohols, which are in turn incorporated in homochiral, chelating bis-oxazolines.[10] The aim of this chapter was to utilize known chemistry for the synthesis of new (and some known) homochiral ligands for coordination and metallosupramolecular chemistry.

The reaction of amino acids with halomethylpyridines and the coordination chemistry of the derived ligands has been extensively studied.[69, 70] The prior work in this area provides a valuable stepping stone towards the synthesis of some new ligands.

The synthesis of an amide bond is one of the most important reactions in amino acid chemistry. Although the synthesis of pyridyl-based ligands via this route have been extensively reported in the literature, there are surprisingly only two reports of metal complexes of these types of ligands.[71]

Although the synthesis of imines from amino acids has been studied in the past, and the study of metal complexes of imines is relatively common, the study of the intersection of these two areas is less common than would be expected.

4.2 N-Alkyl-based Ligands

4.2.1 Introduction

A simple reaction often employed in the synthesis of molecules for use as ligands is the reaction of an amine with an alkyl halide to form an alkyl amine. Interestingly this technique has seldom been applied to the synthesis of ligands from amino acids. One of the simplest of these types of ligands would by *N,N*-bis(2-pyridylmethyl)-L-alanine (**63**). As an illustrative example, **63** could act as a ligand with a number of different bonding modes: the two pyridine sites could chelate to a single metal centre, the two pyridines could bridge different metal centres, the carboxylate group adds an extra possible bridging interaction (see Figure 4.1). There is also precedence for the trisubstituted amine to acts as an additional donor when both the pyridine donors are chelating a single metal centre.[72]

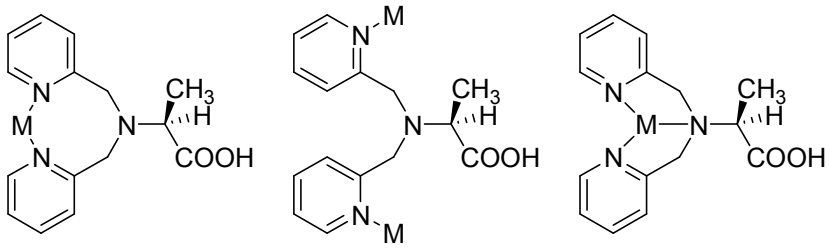


Figure 4.1: The different possible bonding modes of 63, from left to right: chelating a single metal centre, bridging two metal centres, additional chelation by the amine nitrogen. The carboxylate group can add additional bridging interactions to all these bonding modes.

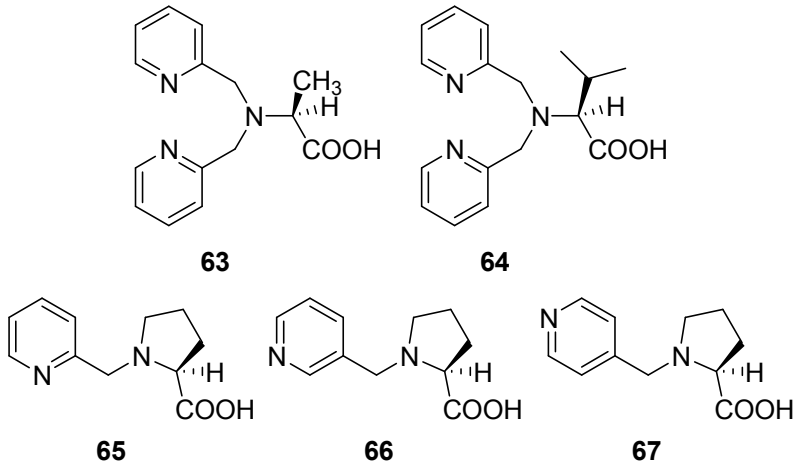
4.2.2 Synthesis

Two different methods were investigated towards the synthesis of these types of molecules: the direct synthesis, reacting the amino acid with an alkyl halide, and the reductive alkylation of the amine using an aldehyde and a reducing agent.[73]

The first method examined was the direct alkylation of amino acids with an alkyl halide. An example of this is the synthesis of **63**. An aqueous solution of picolyl chloride hydrochloride was added to an aqueous solution of L-alanine and sodium hydroxide, and the mixture refluxed overnight. The product was isolated by two different techniques (see Experimental Section for details), and the identity of the product confirmed by comparison of the NMR spectra to literature values.[70]

The second method employed for the synthesis of **63** is that of Levadala and co-workers.[73] This method involves the use of an aldehyde and a reducing agent to reductively alkylate the amine. Compound **63** was successfully synthesized by this method, using pyridine-2-carboxyaldehyde and sodium tris(acetoxy)borohydride. This method is more powerful than the first method, allowing the synthesis of trisubstituted amines with different alkyl groups attached. However, it is technically more complex than the first method, and so was not employed for the synthesis of ligands beyond the initial exploration into the synthesis of **63**.

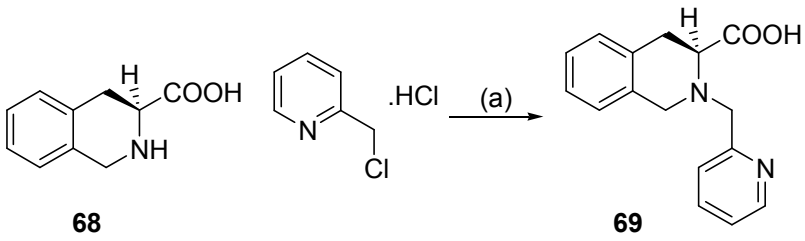
A number of different ligands were synthesized in this series. Compound **63**, mentioned already, was the first to be synthesized. The related compound *N,N*-bis(2-pyridylmethyl)-L-valine (**64**) was synthesized by the same method (see Scheme 4.1). The synthesis of L-proline-based ligands was also investigated, as



Scheme 4.1

these would be different to ligands synthesized from primary amino acids. Using the same method as for the synthesis of **63**, *N*-(2-pyridylmethyl)-L-proline (**65**) was synthesized in good yield (96%). Additionally the related compounds, *N*-(3-pyridylmethyl)-L-proline (**66**) and *N*-(4-pyridylmethyl)-L-proline (**67**), by replacing the picolyl chloride hydrochloride used in the reaction with 3- and 4-chloromethylpyridine hydrochloride respectively (see Scheme 4.1).

The last potential ligand synthesized in this series was based on the artificial amino acid (*S*)-(-)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**68**). The molecule synthesized from **68** is related to **65**, but has a larger ring size, as well as a more constrained geometry, both effects it was hoped would aid in the synthesis of different complexes to those synthesized from **65**. The ligand (**69**) was prepared in the same manner as **65**, by reaction of the amino acid with picolyl chloride in the presence of a base, with a yield of 60% (see Scheme 4.2).



68 **69**

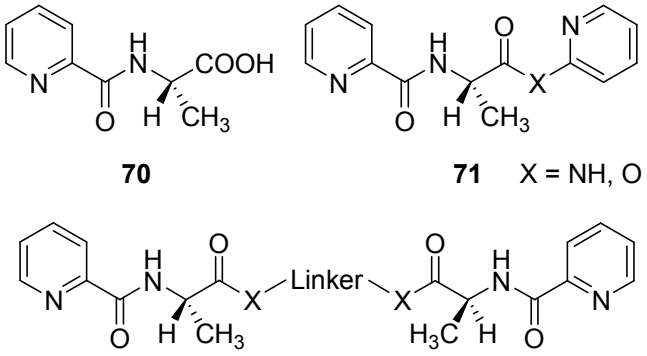
(a) NaOH, H_2O

Scheme 4.2

4.3 Amide-based Ligands

4.3.1 Introduction

One of the most common reactions in peptide chemistry is the formation of an amide bond. This section focuses on the synthesis of ligands from amino acids by formation of amide bonds to attach pyridine rings. The simplest ligand of this type is L-alanine picolinamide (**70**), which has been previously prepared.[74, 75] The obvious extension of this is to add an additional pyridine ring to the other terminus of the molecule to add a further binding site (**71**), or to link together two molecules to provide a symmetric ligand (see Figure 4.2).



70 **71** X = NH, O

Figure 4.2: Molecules 70 and 71. Shown below these is a representation of potential linked derivatives.

4.3.2 Synthesis

The first molecule targeted for synthesis was **70**; the coordination chemistry of this molecule has only been cursorily studied by Reddy and coworkers,[74] so this is an attractive target. The synthetic route to **70** must involve the use of a protected acid group to prevent reaction of the amino acid with itself in any amide synthesis reaction. The starting material chosen in this case was commercially available L-alanine methyl ester, which was reacted with picolinic acid using a mixed carboxylic-carbonic acid anhydride method.[76] The desired

product, L-alanine methyl ester picolinamide (**72**), was isolated in high yield (93%) as a pale yellow oil. Hydrolysis of **72** to **70** was achieved by reaction with 5% lithium hydroxide solution in 3:1 methanol:water, which provided the desired product in near quantitative yield. Slow evaporation of a dichloromethane solution of **70** provided crystals suitable for X-ray crystallography.

Structure of 70

Compound **70** crystallizes in orthorhombic space-group $P2_12_12_1$, with one molecule in the asymmetric unit. There is an intramolecular interaction between the pyridine nitrogen (N6) and the amide hydrogen (H3A) which dictates the orientation of the pyridine ring (see Figure 4.3). The extended structure of **70** features a one-dimensional hydrogen bonded polymer along the *y*-axis, the 2_1 screw axis growing the polymer. The polymer can be viewed as the polar core where the hydrogen bonding occurs, with the non-polar parts of the molecules forming the outside. The difference in size between the methyl and pyridine groups creates pockets, into which the pyridine rings of the polymer chain adjacent in the *z*-direction interdigitate. The pyridine rings have edge to face interactions with adjacent pyridine rings, extending to a plane of such interactions (see Figure 4.4).

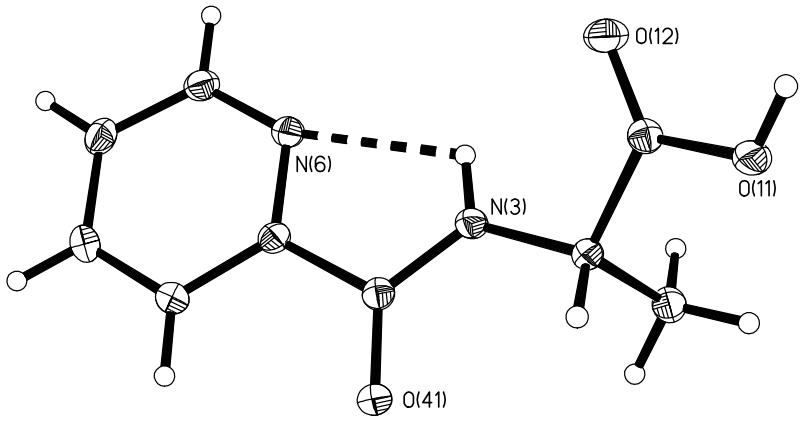


Figure 4.3: A perspective view of the compound 70. The intramolecular hydrogen bond between the pyridine nitrogen and amide is shown as a dashed line. Hydrogen atoms are shown as spheres of arbitrary radius.

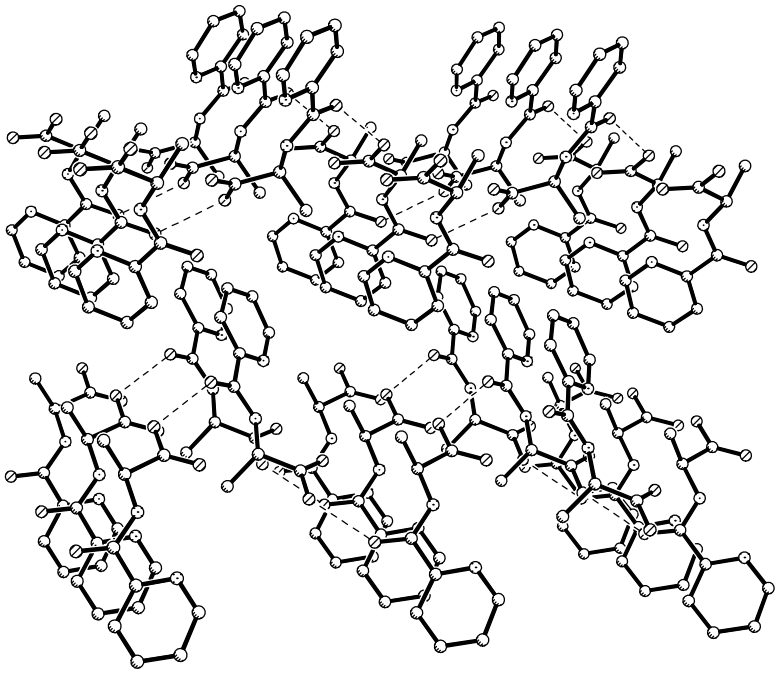
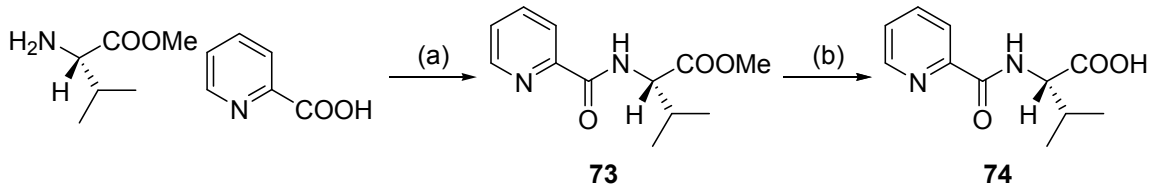


Figure 4.4: A packing diagram showing the π-stacking and hydrogen bonding between molecules of 70.

To test whether this method could be extended to other amino acids, the analogous valine-based molecule was also synthesized. Synthesis of the analogous L-valine methyl ester picolinamide (**73** – see Scheme 4.3) was successful, as was the hydrolysis to L-valine picolinamide (**74**).



73 **74**

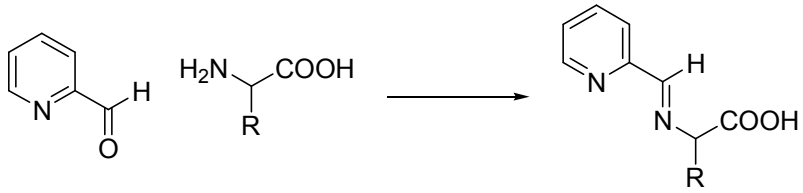
(a) Et_3N, EtOCOCl, $CHCl_3$, PhMe (b) LiOH, H_2O, MeOH

Scheme 4.3

4.4 Imine- and Thiazolidine-based Ligands

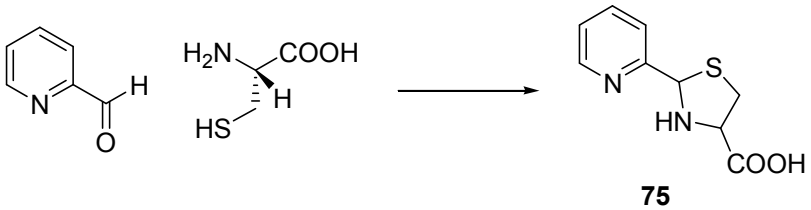
4.4.1 Introduction

The previous two sections of this chapter have investigated the synthesis of ligands from amino acids using two possible derivatisation routes, the alkylation of the amine, and the synthesis of an amide from the amine. This section investigates a third route to the synthesis of ligands from amino acids, again focusing on derivatisation at the amine terminus: the reaction of an amine with an aldehyde to form an imine (see Scheme 4.4). Ligands used to coordinated metal ions are based on this motif are less common than the previous two types, and there are only two reports[77] in the literature of crystal structures of complexes of these types of ligands.



Scheme 4.4

Although the synthesis of imine-based ligands was the aim of this section, during the synthesis of these ligands and of complexes from these ligands, another class of ligands was encountered and investigated. The reaction of cysteine with pyridine-2-carboxaldehyde results in the unexpected synthesis of 2-(2-pyridyl)-4-thiazolidinecarboxylic acid (**75** – see Scheme 4.5). This cyclisation is a known



75

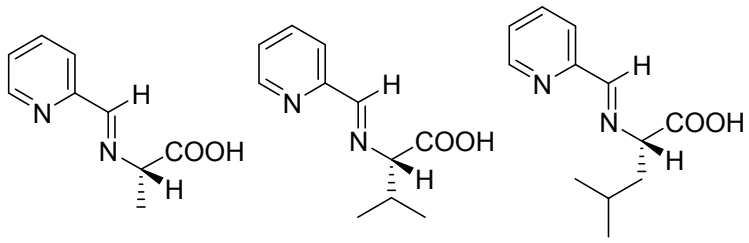
Scheme 4.5

reaction, and this compound,[78-81] as well as some related ones,[79, 81, 82] has been previously reported. This class of ligand is also covered in this section of the chapter.

4.4.1 Synthesis

The ligands in this chapter were synthesized exclusively in solution at the desired concentration, then used directly in the attempted synthesis of complexes, without isolation. Typically the formation of the desired ligand can be monitored by the uptake of the amino acid into a solvent in which it is not normally soluble, indicating reaction has taken place. When complete reaction/dissolution of the amino acid has occurred, the solution is stirred for a further 30 minutes, and then used directly to react with solutions of metal salts.

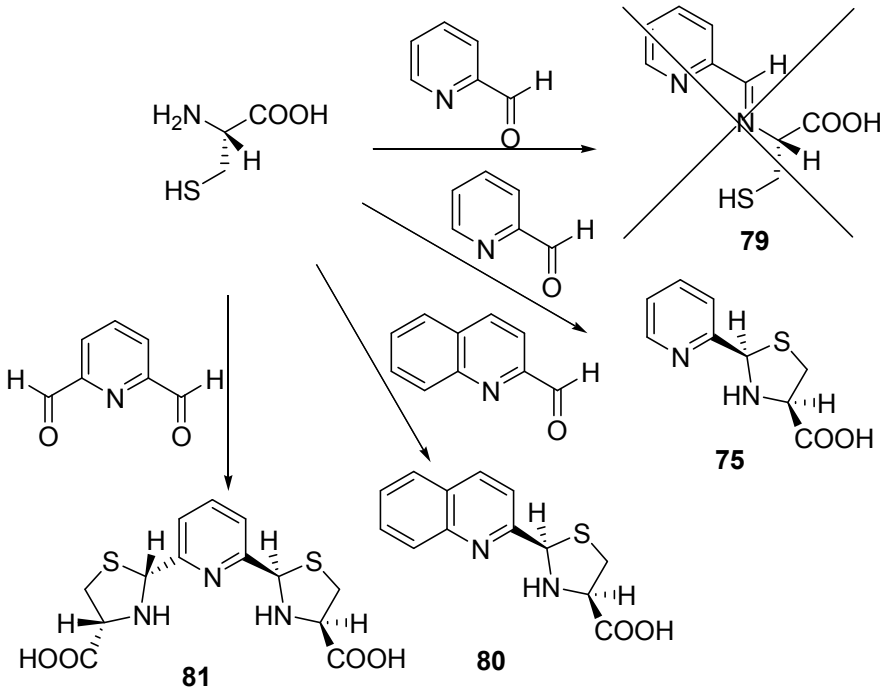
The simplest ligand in this series is (*S*)-2-(2-iminomethylpyridine)-propanoic acid (**76**), and is synthesized from the reaction of pyridine-2-carboxaldehyde with L-alanine in methanol. The solution was used directly for the synthesis of metal complexes. Analogues of this ligand using L-valine (**77**) and L-leucine (**78**) were also synthesized (see Scheme 4.6).



76 **77** **78**

Scheme 4.6

Originally it was intended to synthesize a ligand based on cysteine in this series (**79** – see Scheme 4.7). Instead, as mentioned above, thiazolidine **75** resulted. This lead to a new series of ligands being synthesized, by varying the aldehyde used in the synthesis. Aldehydes used in this way, beyond pyridine-2-



Scheme 4.7

carboxaldehyde, were quinoline-2-carboxaldehyde and pyridine-2,6-dicarboxaldehyde to synthesize ligands **80** and **81** (see Scheme 4.7).

4.5 Summary

In this chapter the synthesis of amino acid based ligands for coordination and metallosupramolecular chemistry was reported. Three different approaches towards this aim were investigated.

N-Alkylation of the amine terminus of the amino acids was studied. The reaction of amino acids with halomethylpyridines resulted in the preparation of a variety of ligands, with a range of donor numbers and configurations.

A more classical approach to amino acid organic chemistry was the synthesis of amide bonds. Again the amine terminus of the amino acid was targeted, and amino acid-picolinamide ligands were synthesized.

The final approach was the *in situ* preparation of imine based ligands. Reaction of the amine with a range of aldehydes led to a number of imine based ligands. The unexpected synthesis of thiazolidine based ligands from cysteine expanded the range and number of ligands explored.

Metal Complexes of Amino Acid Derived Ligands

5.1 Introduction

In this chapter the coordination and supramolecular chemistry of some amino acid based ligands is described. The synthesis of these homochiral ligands was described in the previous chapter.

5.1.1 Thiazolidine-based ligands

Thiazolidines are well known compounds, having been synthesized as early as the 1940s.[83] (2*R*,4*R*)-2-(2-Pyridyl)-4-thiazolidinecarboxylic acid (**75**) has only been reported twice in the literature,[78, 81] and in both cases was used in asymmetric catalysis. The catalytic species was not identified in either report, but was purported to be a complex of rhodium and **75**. No crystal structures of **75** or complexes of **75** have been reported in the literature, although a crystal structure of the ethyl ester of **75** has been reported.[84]

5.1.2 Amide-based ligands

Although a range of ligands based on this concept have been crystallized,[85] only a small number of complexes have been examined by X-ray crystallography.[86] No complexes of **72** or the hydrolyzed derivative **70** have been reported in the literature.

5.1.3 N-Alkyl-based Ligands

No complexes of ligand **65** have been previously reported in the literature, although Bernauer and co-workers[87] have reported extensively on a related C_2 symmetric ligand (see Figure 5.1). This ligand is similar to **65** in that it has a proline ring with an attached pyridylmethyl, however in the work of Bernauer a

second proline ring is attached on the other side of the pyridine ring, so the coordination chemistry will not be directly comparable.

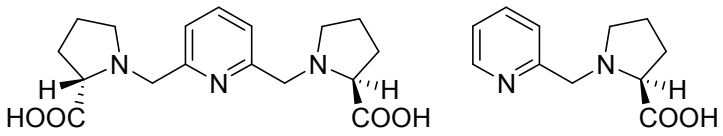


Figure 5.1: The ligand synthesized by Bernauer and co-workers on the left, and ligand 65 on the right.

5.2 Complexes

5.2.1 Complexes of Thiazolidine-based ligands

Synthesis of the Complexes

Complexes **82**, **83**, **84**, **85** and **86** were all synthesized in the same manner. A solution of ligand **75** in 2:1 methanol:water was added to a solution of half an equivalent of the appropriate metal salt in water. Crystals were formed upon standing of the solution. Complex **82** was synthesized with a yield of 20%, with hexa(aqua)cobalt(II) nitrate as the metal salt. Complex **83** was synthesized with cobalt(II) bromide as the metal salt with a yield of 23%. Complex **84** was synthesized in a yield of 55%, with hexa(aqua)nickel(II) nitrate as the metal salt. Complex **85** was synthesized using hexa(aqua)nickel(II) sulfate as the metal salt with a yield of 55%. Complex **85** could also be isolated from the reaction of a number of other nickel(II) metal salts. An example of this is the reaction of nickel(II) bromide trihydrate; the majority of the crystals isolated from this reaction had the same unit cell as **85**, and so were not further analysed. A small rosette of crystals, with a different morphology, had a different unit cell, and proved to be a different complex: complex **86** was isolated with a yield of 14%.

The synthesis of a number of other complexes related to these was attempted. Reaction of a range of metal salts with ligands **80** and **81** was attempted. Unfortunately neither of these ligands led to crystalline products.

Structure of 82

Complex **82** crystallizes in monoclinic space group $P2_1$, as a 2:1 ligand:metal complex. Each ligand is coordinated to the cobalt centre through the pyridine nitrogen, amine nitrogen and an oxygen of the carboxylate, with a facial

arrangement of the donors (see Figure 5.2). The pyridines of the two different ligands have a *trans* relationship, while both the amine and carboxylate have a *cis* relationship to each other. The cobalt centre is in the 3+ oxidation state, with two anionic ligands coordinated. The charge balance is accounted for by a non-coordinated nitrate anion. The asymmetric unit is completed by three water solvate molecules. Both the ligands have the same *R,R* stereochemistry. The presence of 3 water molecules, as well as both hydrogen bonding acceptors and donors being present on the complex itself, leads to 10 unique hydrogen bonds

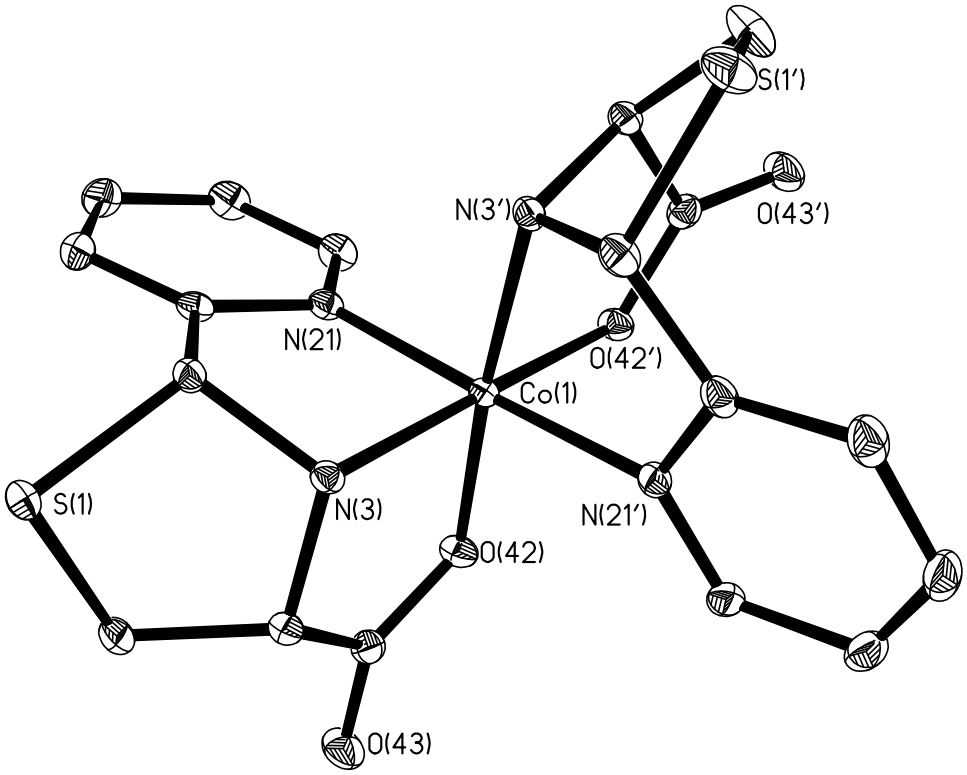


Figure 5.2: A perspective view of complex 82, water molecules, the nitrate anion and hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): Co(1)-N(3) 1.9539(13), Co(1)-N(21) 1.9257(13), Co(1)-O(42) 1.8923(11), Co(1)-N(3') 1.9568(13), Co(1)-N(21') 1.9356(14), Co(1)-O(42') 1.8991(11), N(3)-Co(1)-N(21) 83.46(6), N(3)-Co(1)-O(42) 87.20(5), N(3)-Co(1)-N(3') 96.45(5), N(3)-Co(1)-N(21') 96.24(5), N(3)-Co(1)-O(42') 175.86(5), N(21)-Co(1)-O(42) 89.58(5), N(21)-Co(1)-N(3') 93.36(5), N(21)-Co(1)-N(21') 177.23(6), N(21)-Co(1)-O(42') 94.50(5), O(42)-Co(1)-N(3') 175.55(6), O(42)-Co(1)-N(21') 93.16(5), O(42)-Co(1)-O(42') 89.18(5), N(3')-Co(1)-N(21') 83.94(6), N(3')-Co(1)-O(42') 87.25(5), N(21')-Co(1)-O(42') 85.97(5).

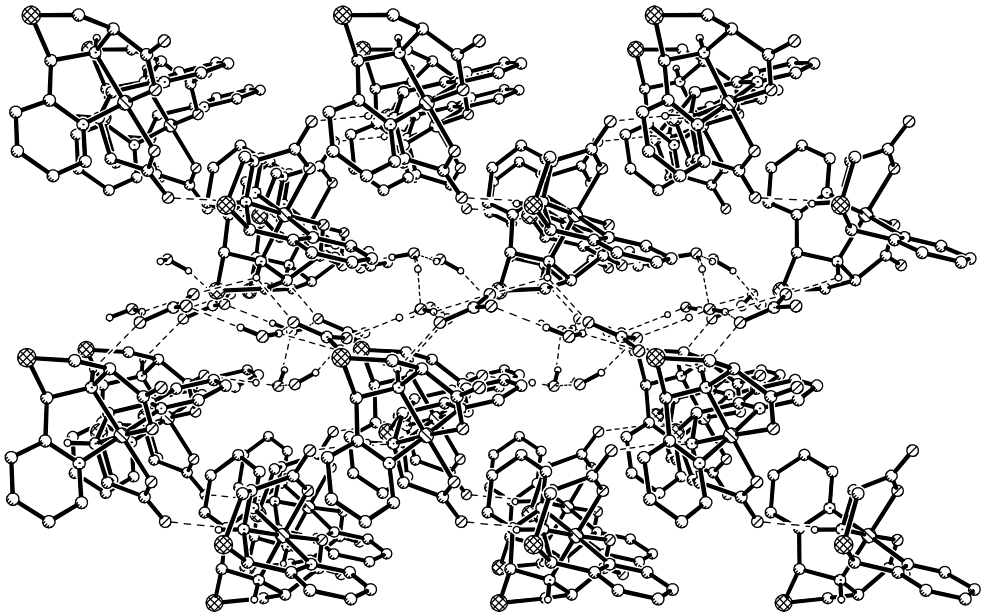


Figure 5.3: A packing diagram of complex 82. Two layers of the complex can be seen here, with the intermediate water molecules and nitrate anion hydrogen bonded between the layers. Non-hydrogen bonding hydrogen atoms are omitted for clarity.

being present in the structure. This large number of hydrogen bonds leads to a complicated three dimensional hydrogen bonding network. Although this network is difficult to describe clearly in detail, a simplified representation is of layers in the *xy*-plane of the cobalt complex, hydrogen bonded to each other, separated by layers of hydrogen bonded water molecules and nitrate anions (see Figure 5.3). The two layers are also hydrogen bonded to each other, extending the hydrogen bonding network in three dimensions.

Structure of 83

Compound **83** crystallizes in orthorhombic space group $P2_12_12$ as a 2:1 ligand:metal complex. Each ligand is coordinated to the cobalt centre through the pyridine nitrogen, amine nitrogen and an oxygen of the carboxylic acid (see Figure 5.4). This complex has the same facial arrangement of donors as the

previous complex, as well as the same arrangement of donors between the two ligands. The cobalt centre is in the 3+ oxidation state, with two anionic ligands coordinated and a non-coordinated, disordered bromide anion, which is hydrogen bonded to one of the amine groups. The hydrogen bonding in this complex is simpler than that of the previous complex. Each complex has a hydrogen bond to the bromide anion, as well as the symmetry related bromide of an adjacent complex, both from the same amine group. The complementary

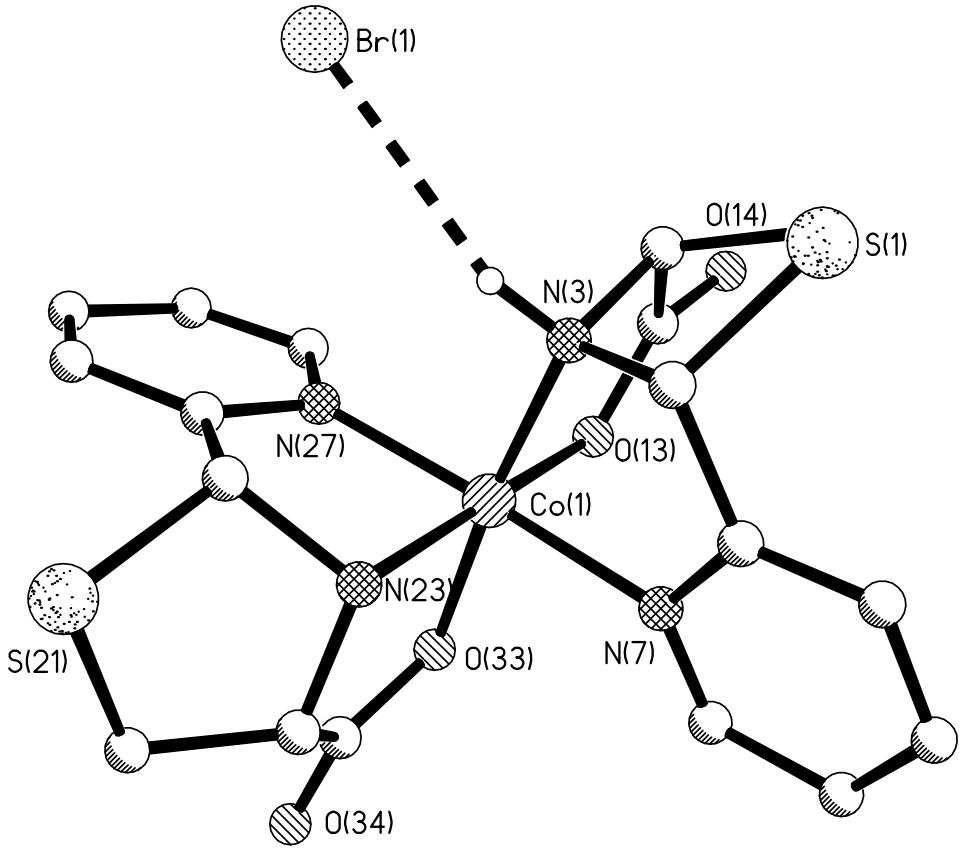


Figure 5.4: A perspective view of complex 83. Non-hydrogen bonded hydrogens and the minor component of the bromide disorder are omitted for clarity. The dashed line represents a hydrogen bond. Selected bond lengths (Å) and angles (°): Co(1)-N(3) 1.904(11), Co(1)-N(7) 1.957(9), Co(1)-O(13) 1.926(9), Co(1)-N(23) 1.938(7), Co(1)-N(27) 1.958(9), Co(1)-O(33) 1.905(8), N(3)-Co(1)-N(7) 84.4(4), N(3)-Co(1)-O(13) 87.9(5), N(3)-Co(1)-N(23) 97.8(5), N(3)-Co(1)-N(27) 96.1(5), N(3)-Co(1)-O(33) 173.6(4), N(7)-Co(1)-O(13) 89.7(4), N(7)-Co(1)-N(23) 92.9(4), N(7)-Co(1)-N(27) 176.5(4), N(7)-Co(1)-O(33) 91.9(4), O(13)-Co(1)-N(23) 173.9(5), O(13)-Co(1)-N(27) 93.8(4), O(13)-Co(1)-O(33) 86.9(4), N(23)-Co(1)-N(27) 83.6(3), N(23)-Co(1)-O(33) 87.5(3), N(27)-Co(1)-O(33) 87.9(4).

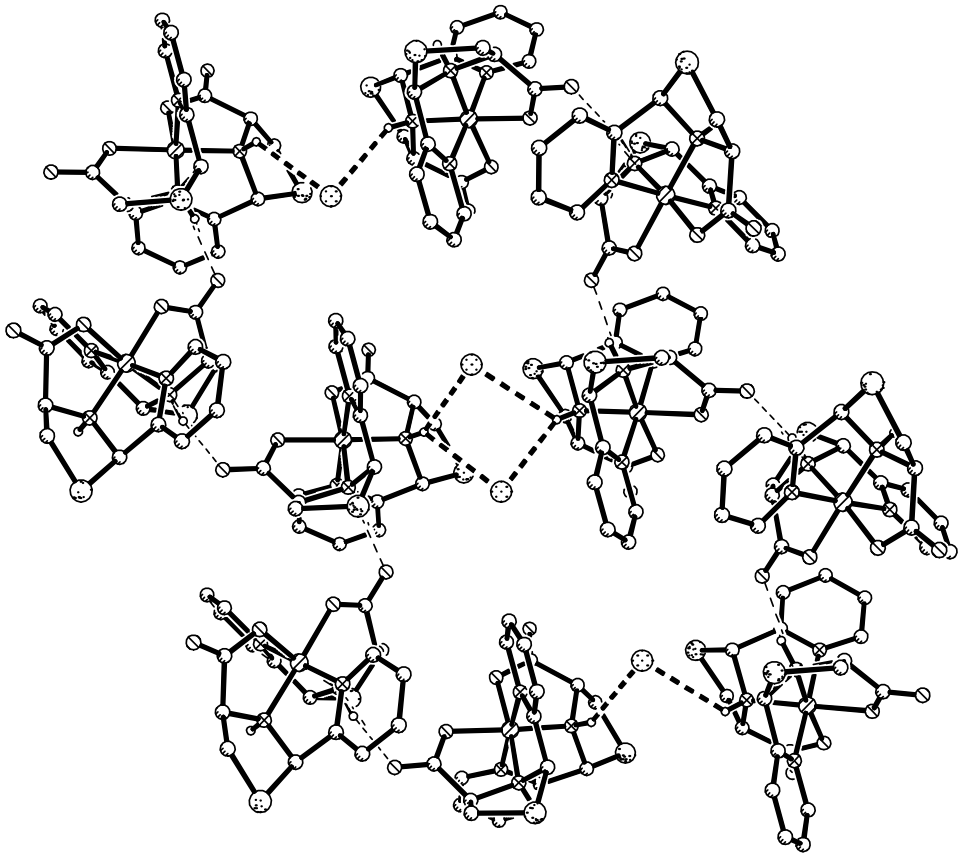


Figure 5.5: A packing diagram of complex 83, showing the (6,3) hydrogen bonding network in the *xy*-plane.

hydrogen bonds to the amine of the adjacent complex form a dimeric structure. These are linked to adjacent dimeric structures by hydrogen bonding of the other amine present in the complex to one of the carboxylate oxygens of another adjacent complex. The combination of these two hydrogen bonding interactions results in a two-dimensional (6,3) hydrogen bonded network in the *xy*-plane (see Figure 5.5). There is no notable interaction between adjacent planes. Unfortunately this may not represent the true hydrogen bonding situation within the structure. Due to poor crystal quality and a high level of background electron density, believed to be due to disordered solvent molecules, the SQUEEZE routine from PLATON[88] was applied. This removes the residual electron density

from disordered solvent molecules within the structure, which may mask any further hydrogen bonding within the structure.

Structure of 84

Complex **84** crystallizes in monoclinic space group $P2_1$, as a 2:1 metal:ligand complex. Each ligand is coordinated to the nickel centre through the pyridine nitrogen, amine nitrogen and an oxygen of the carboxylic acid (see Figure 5.6). This complex has the same facial arrangement of donors as the previous

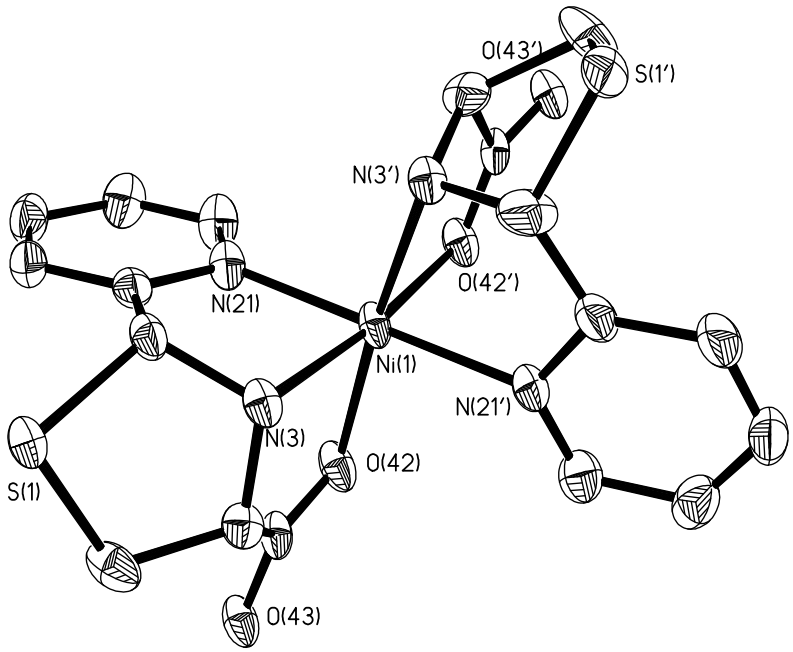


Figure 5.6: A perspective view of the nickel complex in structure 84. Hydrogen atoms and the nitrate anion are omitted for clarity. Selected bond lengths (Å) and angles (°): Ni(1)-N(3) 2.0890(18), Ni(1)-N(21) 2.0566(19), Ni(1)-O(42) 2.0927(16), Ni(1)-N(3') 2.0960(18), Ni(1)-N(21') 2.0517(19), Ni(1)-O(42') 2.0902(16), N(3)-Ni(1)-N(21) 81.35(8), N(3)-Ni(1)-O(42) 82.07(7), N(3)-Ni(1)-N(3') 97.18(7), N(3)-Ni(1)-N(21') 99.55(7), N(3)-Ni(1)-O(42') 173.22(7), N(21)-Ni(1)-O(42) 86.20(7), N(21)-Ni(1)-N(3') 99.07(7), N(21)-Ni(1)-N(21') 178.93(8), N(21)-Ni(1)-O(42') 92.26(7), O(42)-Ni(1)-N(3') 174.53(7), O(42)-Ni(1)-N(21') 93.35(7), O(42)-Ni(1)-O(42') 99.88(6), N(3')-Ni(1)-N(21') 81.41(8), N(3')-Ni(1)-O(42') 81.50(6), N(21')-Ni(1)-O(42') 86.86(7).

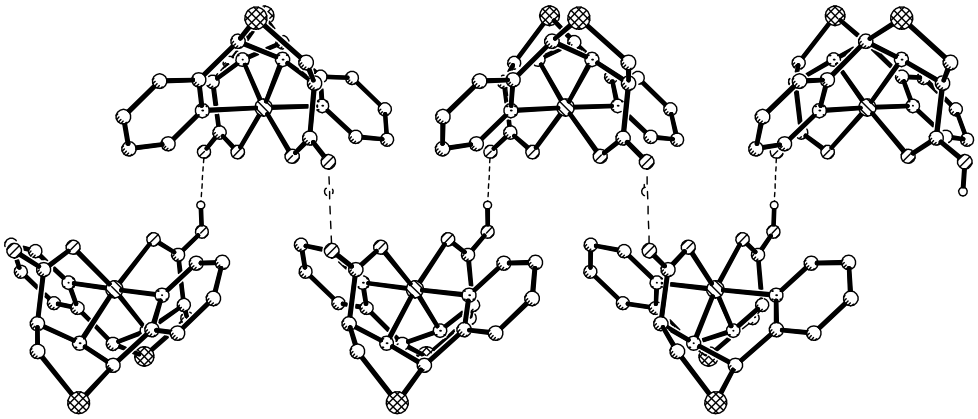


Figure 5.7: The one-dimensional hydrogen bonded polymer present in structure 85. Non-hydrogen bonded hydrogen atoms are omitted for clarity.

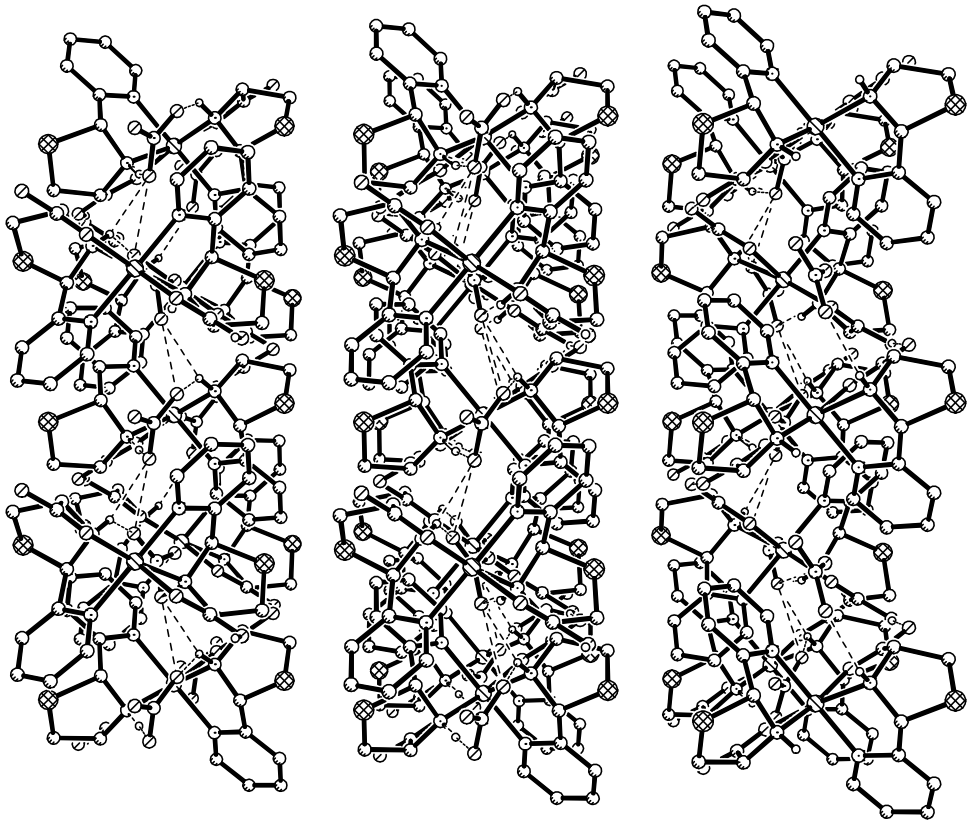


Figure 5.8: A packing diagram of structure 84 showing the hydrogen bonding between nitrate anions and chains to form two-dimensional networks in the *yz*-plane and stacking in the *x*-direction.

complexes, as well as the same arrangement of donors between the two ligands. There is one nitrate anion present in the structure, with the nickel in the 2+ oxidation state, meaning one of the carboxylates is protonated. When attempts were made to determine which carboxylate group the proton was located on by examining the electron density difference map, both had peaks of equal height in close proximity with an appropriate geometry. Initially the proton was assigned as being disordered over both sites, although it soon became apparent that this was a simplistic representation of the situation. Examination of the hydrogen bonding in the structure reveals a one dimensional chain, which is formed by hydrogen bonding between symmetry equivalent complexes along the *y*-axis (see Figure 5.7). The alternating complexes are related by the 2_1 screw axis, with hydrogen bonding between adjacent carboxylic acid groups. The proton is disordered between the two carboxylic acids in the asymmetric unit, which leads to it being disordered between those of adjacent complexes as part of the hydrogen bonding network. The amines of each complex are both hydrogen bonded to the same nitrate anion and there is an additional hydrogen bond to an adjacent chain, linking them together to form a two-dimensional hydrogen bonded network in the *yz* plane. These networks stack in the *x*-direction (see Figure 5.8)

Structure of 85

Complex **85** crystallizes in orthorhombic space group $P2_12_12_1$, as a 2:1 ligand:metal complex. The arrangement of donors and ligands is identical to that of the previous three structures (see Figure 5.9). In this structure both carboxylate groups are deprotonated, and there is no other anion present; the nickel is in the 2+ oxidation state. The asymmetric unit is completed by a water molecule, which is hydrogen bonded to one of the carboxylate groups of the complex. There is further hydrogen bonding between adjacent complexes and water molecules which lead to the extended hydrogen bonding network. Each complex is hydrogen bonded to the four adjacent complexes in the *xy*-plane. All four of these complexes are related by translation, and the hydrogen bonds

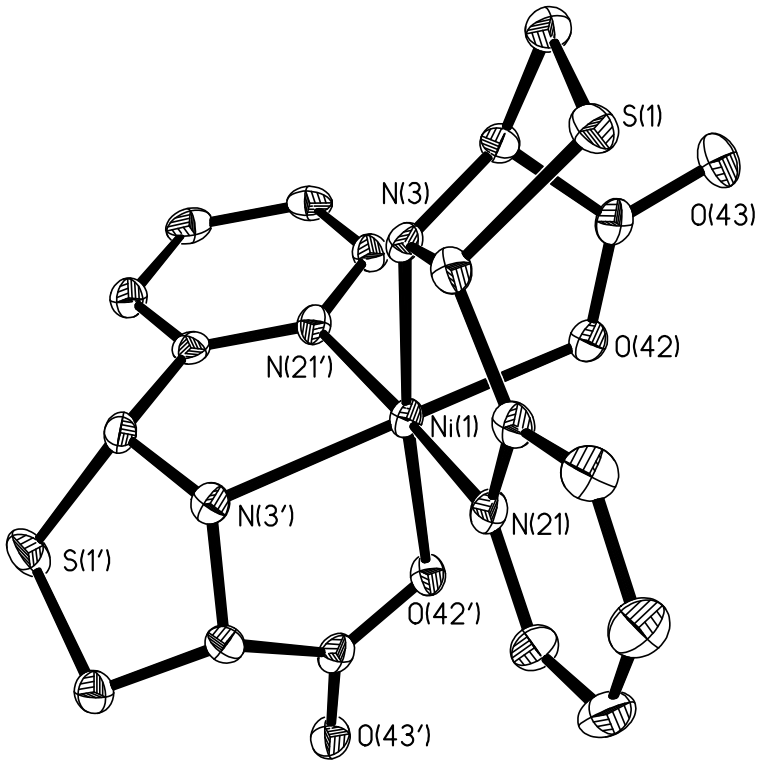


Figure 5.9: A perspective view of complex 85. Hydrogen atoms and the water molecule are omitted for clarity. Selected bond lengths and angles: Ni(1)-N(3) 2.093(2), Ni(1)-N(21) 2.0683(18), Ni(1)-O(42) 2.0658(16), Ni(1)-N(3') 2.1418(19), Ni(1)-N(21') 2.0890(18), Ni(1)-O(42') 2.0454(16), N(3)-Ni(1)-N(21) 81.70(8), N(3)-Ni(1)-O(42) 80.41(7), N(3)-Ni(1)-N(3') 104.37(8), N(3)-Ni(1)-N(21') 93.34(7), N(3)-Ni(1)-O(42') 174.19(7), N(21)-Ni(1)-O(42) 90.54(7), N(21)-Ni(1)-N(3') 94.97(7), N(21)-Ni(1)-N(21') 172.51(8), N(21)-Ni(1)-O(42') 96.00(7), O(42)-Ni(1)-N(3') 173.16(7), O(42)-Ni(1)-N(21') 94.18(7), O(42)-Ni(1)-O(42') 94.31(7), N(3')-Ni(1)-N(21') 80.77(7), N(3')-Ni(1)-O(42') 81.11(7), N(21')-Ni(1)-O(42') 89.45(7).

are between the amine hydrogens and carboxylate oxygens. This forms a (4,4) net in this plane (see Figure 5.10). The water molecule (hydrogen bonded to one carboxylate group) is further hydrogen bonded via the other hydrogen to an adjacent symmetry equivalent complex via one of the sulfur atoms. The interaction between the complexes is not limited to hydrogen bonding: there is π-stacking between the pyridine rings of the layers. The pyridine rings interdigitate, but are offset in the *z*-direction, not fully overlapping (see Figure 5.11). The rings are also not parallel, with the distances between adjacent rings ranging from

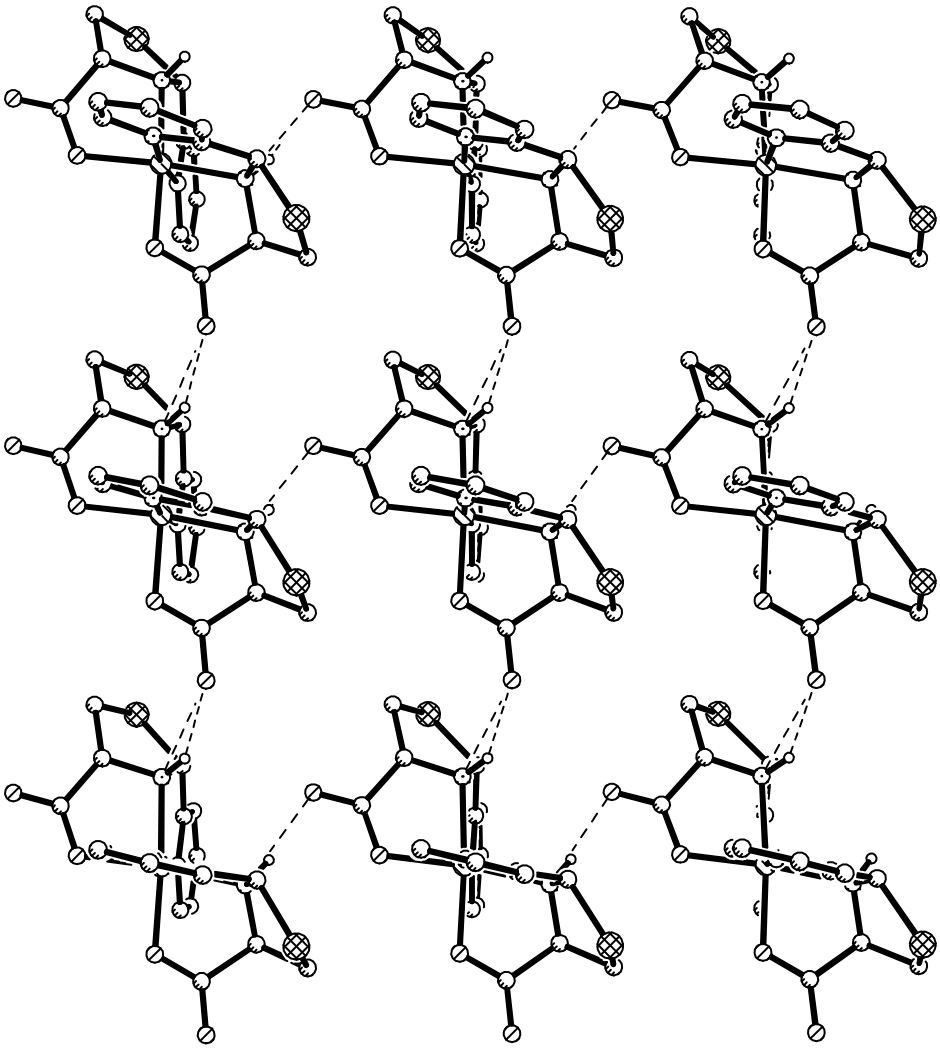


Figure 5.10: The (4,4) net formed from hydrogen bonding between the complexes and water molecules in the *xy*-plane.

3.706 to 4.837 Å. These two layers form a bilayer which is not hydrogen bonded any further in the *z*-direction. The interaction with adjacent bilayers is restricted to π-stacking; similar to the intra-bilayer π-stacking, the interdigitating pyridine rings are offset in the *z*-direction and are not parallel. The π-stacking in this case is tighter, with ring to ring distances ranging from 3.585 to 3.734 Å.

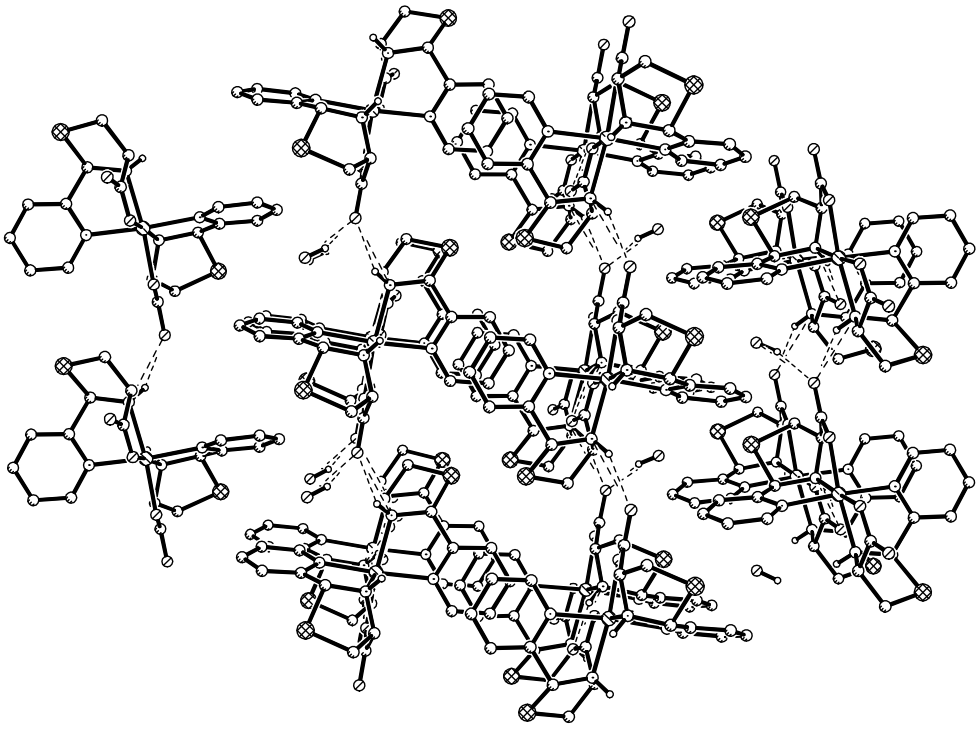


Figure 5.11: A perspective view showing how the hydrogen bonded networks stack in the *z*-direction. The π-stacking between pyridine rings of adjacent networks can clearly be seen here.

Structure of 86

Complex **86** crystallizes in monoclinic space group $P2_1$, as a 2:1 ligand:metal complex. Again the arrangement of donors and ligands is identical to that of the previous structures (see Figure 5.12). In this structure there is one bromide anion, so it is assumed that only one of the ligands is anionic. The hydrogen atom could not be located in the electron density difference map, and so was not initially assigned. Examination of the extended structure reveals an intermolecular relationship between molecules almost identical to that observed in complex **85**, indicating a one-dimensional hydrogen bonded chain along the *y*-axis. This would indicate that the protons are disordered between the carboxylate groups of adjacent complexes, as in complex **84**, accounting for the

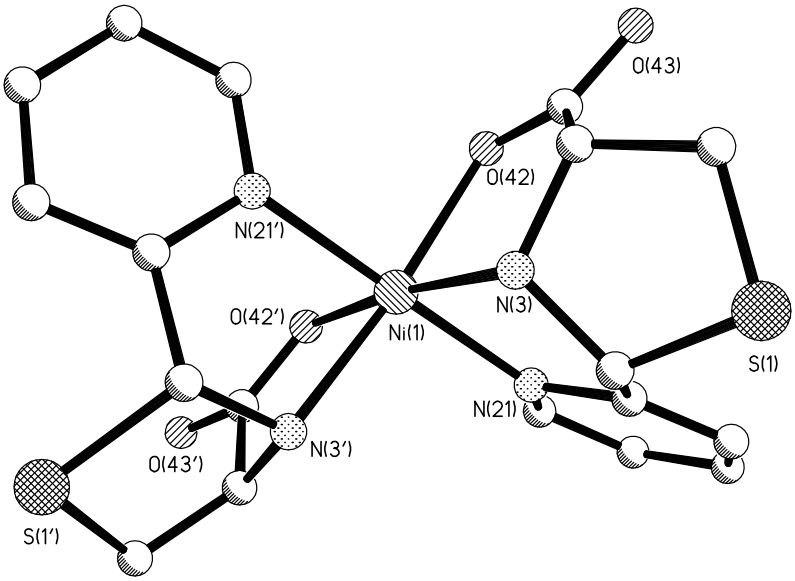


Figure 5.12: A perspective view of 86. Hydrogen atoms and the counter ion are omitted for clarity. Selected bond lengths (Å) and angles (°): Ni(1)-N(3) 2.080(7), Ni(1)-N(21) 2.038(7), Ni(1)-O(42) 2.094(6), Ni(1)-N(3') 2.079(7), Ni(1)-N(21') 2.039(7), Ni(1)-O(42') 2.079(6), N(3)-Ni(1)-N(21) 81.7(3), N(3)-Ni(1)-O(42) 81.8(3), N(3)-Ni(1)-N(3') 98.2(3), N(3)-Ni(1)-N(21') 100.4(3), N(3)-Ni(1)-O(42') 172.9(3), N(21)-Ni(1)-O(42) 86.0(2), N(21)-Ni(1)-N(3') 99.7(3), N(21)-Ni(1)-N(21') 177.4(3), N(21)-Ni(1)-O(42') 91.4(3), O(42)-Ni(1)-N(3') 174.3(3), O(42)-Ni(1)-N(21') 92.6(2), O(42)-Ni(1)-O(42') 99.5(2), N(3')-Ni(1)-N(21') 81.7(3), N(3')-Ni(1)-O(42') 81.2(3), N(21')-Ni(1)-O(42') 86.6(3).

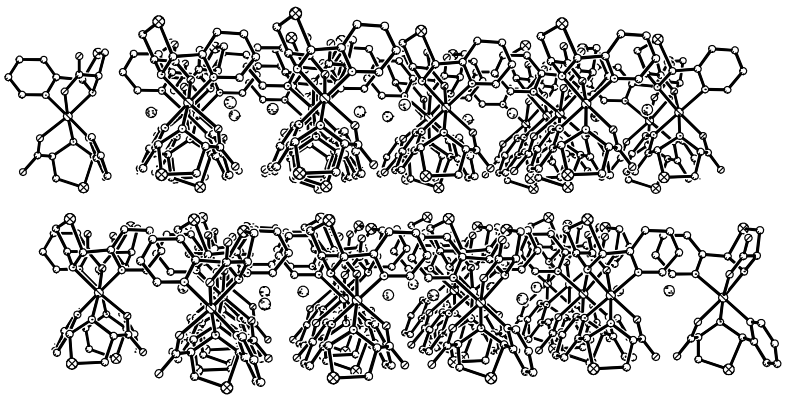


Figure 5.13: A packing diagram showing how the bromide anions sit in channels between the complexes. All hydrogens are omitted for clarity.

charge balance. Similar to the position of the nitrate in complex **84**, the bromide anion is hydrogen bonded to both amine hydrogens of the complex. The bromide anions sit in channels between adjacent polymer chains in the *z*-direction (see Figure 5.13).

5.2.2 Complexes of Pyridyl-Amide-based ligands

Synthesis of the Complexes

Complex **87** was synthesized by reacting two equivalents of ligand **72** dissolved in acetonitrile with one equivalent of copper nitrate trihydrate, also dissolved in acetonitrile. The solution immediately darkened. The solution was divided up and a range of non-polar solvents diffused into the different solutions to crystallize the product. Slow diffusion of diethyl ether into the solution provided crystals suitable for X-ray crystallography in a yield of 80%. Initial synthesis of the silver complex **88** was almost identical the synthesis of complex **87**, however the solution was kept light free, and in this case the solvent which resulted in eventual crystallisation was ethyl acetate. This complex required almost complete evaporation of all solvent before the two crystals were formed. Unfortunately there was insufficient amount of this complex to study it beyond X-ray crystallography.

Structure of 87

Complex **87** crystallizes in monoclinic space group $P2_1$, as a 2:1 ligand:metal complex. The asymmetric unit consists of only the metal centre, coordinated to two ligands and two nitrate anions (see Figure 5.14). Both ligands chelate the copper centre through the pyridine nitrogen and the amide oxygen, with a bite angle of 82.57(11)°. Both ligands are coordinated in the same plane, with the nitrate anions occupying the axial positions. The copper oxygen bonds to the nitrate anions are Jahn-Teller distorted as is expected in such complexes:

2.405(3) and 2.425(3) Å compared to the 1.970(3)-1.991(2) Å for the equatorial

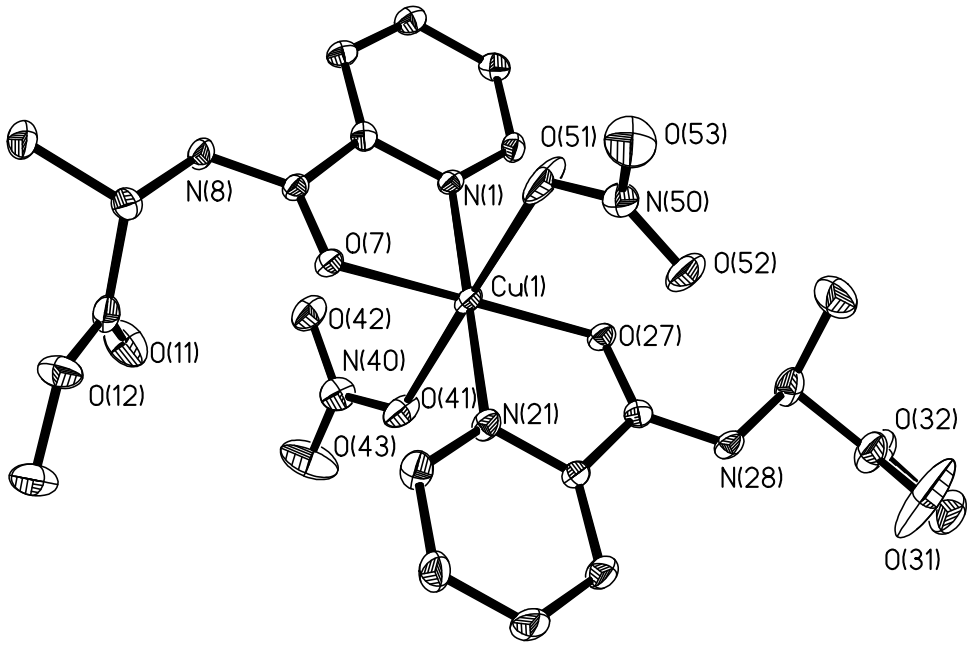


Figure 5.14: A perspective view of complex 87. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Cu(1)-N(1) 1.970(3), Cu(1)-O(7) 1.991(2), Cu(1)-N(21) 1.970(3), Cu(1)-O(27) 1.988(2), Cu(1)-O(41) 2.405(3), Cu(1)-O(51) 2.425(3), N(1)-Cu(1)-O(7) 82.57(11), N(1)-Cu(1)-N(21) 179.01(14), N(1)-Cu(1)-O(27) 97.88(11), N(1)-Cu(1)-O(41) 96.77(10), N(1)-Cu(1)-O(51) 84.61(12), O(7)-Cu(1)-N(21) 96.73(11), O(7)-Cu(1)-O(27) 179.54(13), O(7)-Cu(1)-O(41) 91.25(9), O(7)-Cu(1)-O(51) 89.06(10), N(21)-Cu(1)-O(27) 82.82(11), N(21)-Cu(1)-O(41) 83.94(11), N(21)-Cu(1)-O(51) 94.68(12), O(27)-Cu(1)-O(41) 88.63(9), O(27)-Cu(1)-O(51) 91.05(10), O(41)-Cu(1)-O(51) 178.61(12).

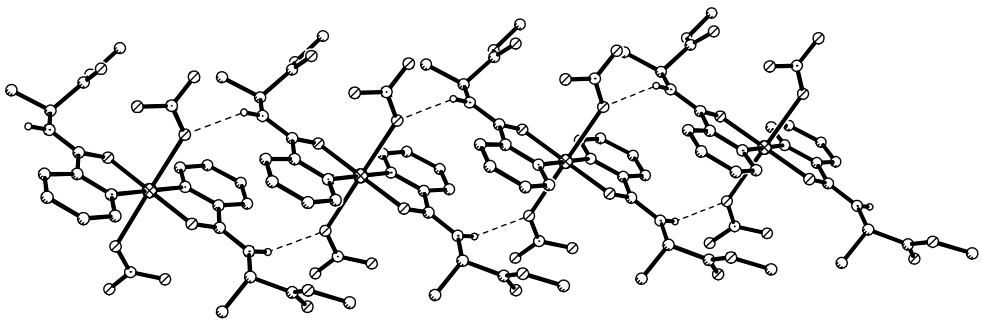


Figure 5.15: The one-dimensional hydrogen bonded polymer along the *x*-axis.

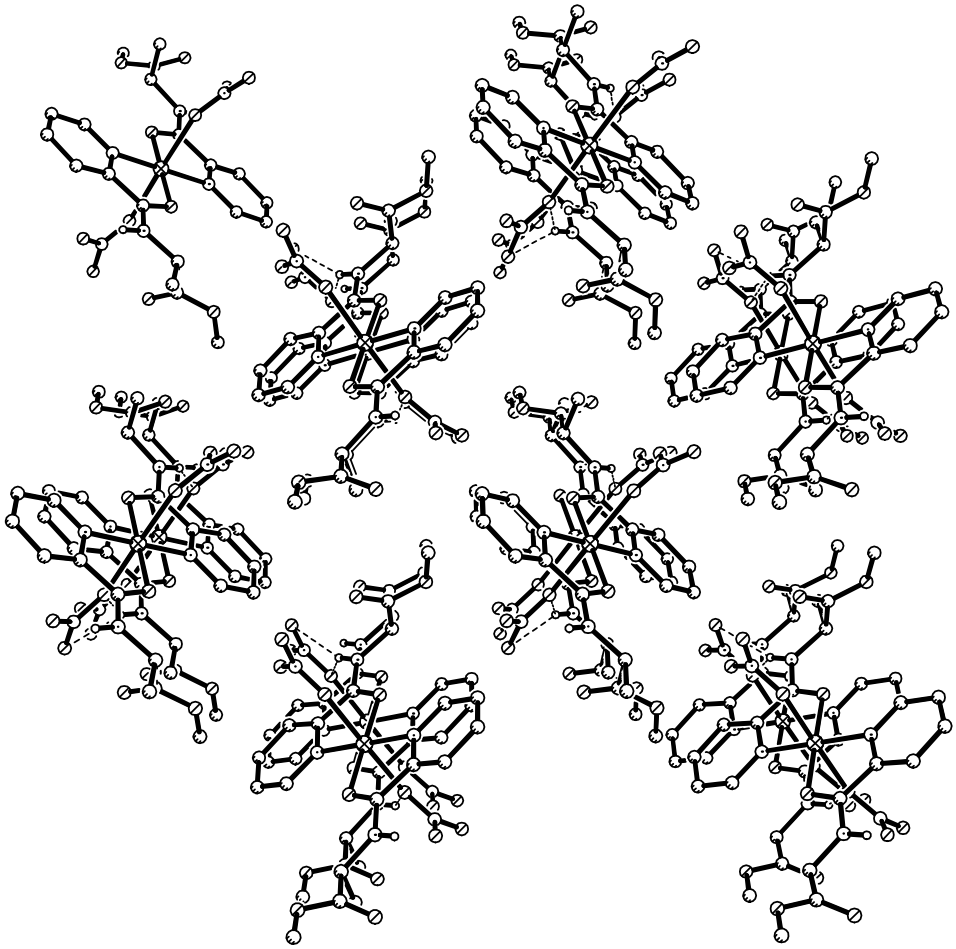


Figure 5.16: The packing of the hydrogen bonded polymers.

ligands. The relative conformation of the two ligands is different (see Figure 5.14), so although there is a rotational relationship between them, they are not related by any true symmetry. Each complex has four hydrogen bonds; these are between each amide hydrogen and the nitrate anion of an adjacent complex, as well as the complementary hydrogen bond from the nitrates to the amide protons of the adjacent complexes (see Figure 5.15). The complexes are related by translation in the *x*-direction, with the polymer chains stacking in the *y*- and *z*-directions (see Figure 5.16).

Structure of 88

Complex **88** crystallizes in orthorhombic space group $P2_12_12_1$, as a 2:1 ligand:metal complex. The asymmetric unit consists of the metal centre chelated by the pyridine nitrogen and amide oxygen of both ligands, and is completed by the perchlorate counter ion, which is hydrogen bonded to the complex (see Figure 5.17). The geometry of the silver centre is distorted tetrahedral, with the bite angles of the chelate rings being 71.15(5) and 71.44(5)°, while the other angles around the silver centre range from 105.73(4) to 151.11(5)°. This wide range is due to the constrained geometry of the chelate ring, which in turns causes the other angles to widen. In this complex the bonds between the pyridine nitrogens and the silver centre (2.2147(15) and 2.2280(15) Å) are shorter than those between the amide oxygens and the silver centre (2.4520(12) and 2.4741(13) Å). The hydrogen bonding of the perchlorate anion to an adjacent complex leads to a one-dimensional hydrogen bonded chain (see

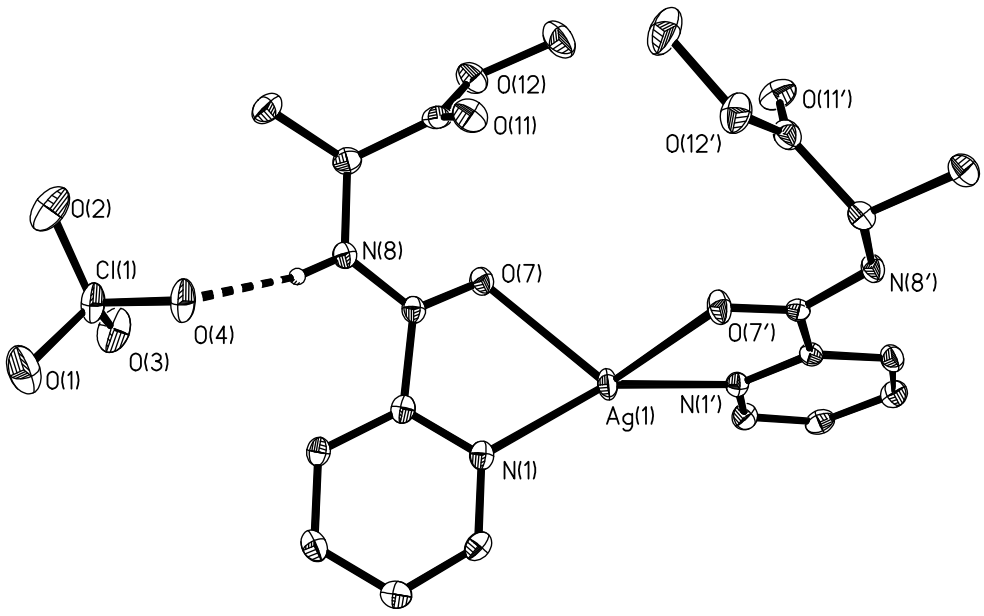


Figure 5.17: The asymmetric unit of 88. The hydrogen bonding proton is represented by a sphere of arbitrary radius. Other hydrogens are omitted for clarity. Selected bond lengths (Å) and angles (°): Ag(1)-N(1) 2.2280(15), Ag(1)-O(7) 2.4741(13), Ag(1)-N(1') 2.2147(15), Ag(1)-O(7') 2.4520(12), N(1)-Ag(1)-O(7') 71.44(5), N(1)-Ag(1)-N(1') 151.11(5), N(1)-Ag(1)-O(7') 125.32(5), O(7)-Ag(1)-N(1') 131.13(5), O(7)-Ag(1)-O(7') 105.73(4), N(1')-Ag(1)-O(7') 71.15(5).

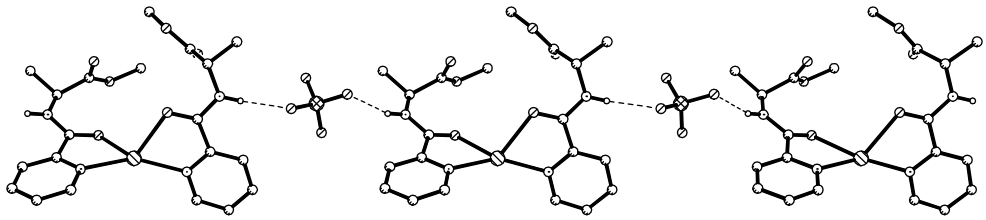


Figure 5.18: The one-dimensional hydrogen bonding chain along the *y*-axis.

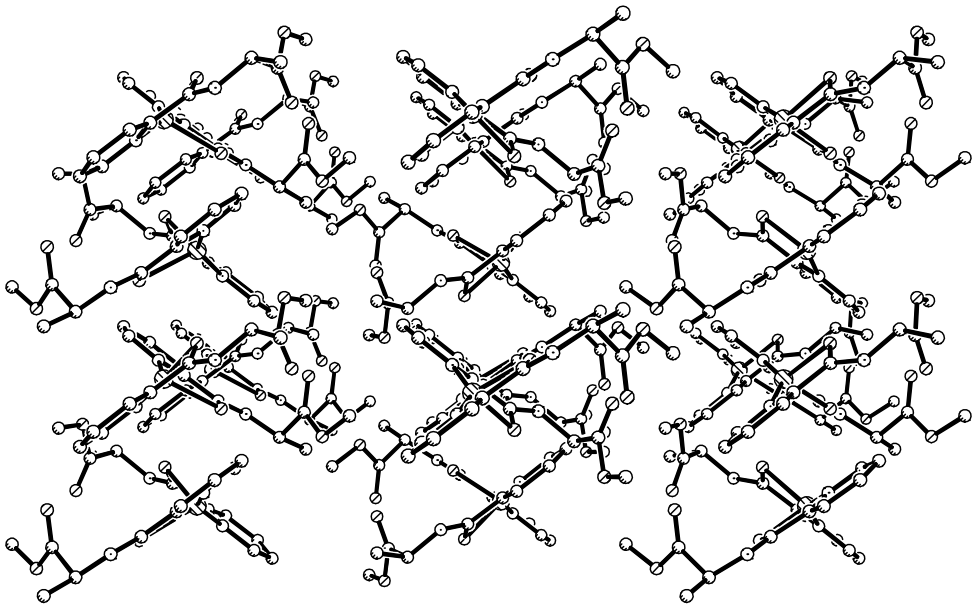


Figure 5.19: A perspective view of 88 looking down the *y*-axis showing the π-stacking present in the complex.

Figure 5.18). The complexes of the chain are related by translation along the *y*-axis. Along the *x*-axis there is π-stacking interactions between adjacent, screw-axis related, complexes. Each pyridine ring has an offset π-stacking interaction with the pyridine ring of an adjacent complex; distances between the pyridine rings are approximately 3.4 Å (see Figure 5.19). The other adjacent complex does not π-stack with the pyridine ring; instead the amino acid tail is positioned over the pyridine ring. Along the *z*-axis the complexes stack simply, with the amino acid tail groups filling the gaps between adjacent complexes in this direction.

5.2.3 Complexes of N-Pyridyl-Amino Acid-based Ligands

Synthesis of the complexes

Only one complex was synthesized from this series of ligands, despite a large array of attempted syntheses with different metal salts and solvent systems. The reaction of two equivalents of ligand **65** in methanol with one equivalent of cobalt(II) bromide in acetonitrile resulted in an orange solution. Slow evaporation of the solution furnished thin needle-like crystals of complex **89** suitable for X-ray crystallography. Although the structure could be identified it could not be fully refined as it was of poor quality due to twinning of the crystal. Numerous crystals were examined in an attempt to find a high quality one, and several were

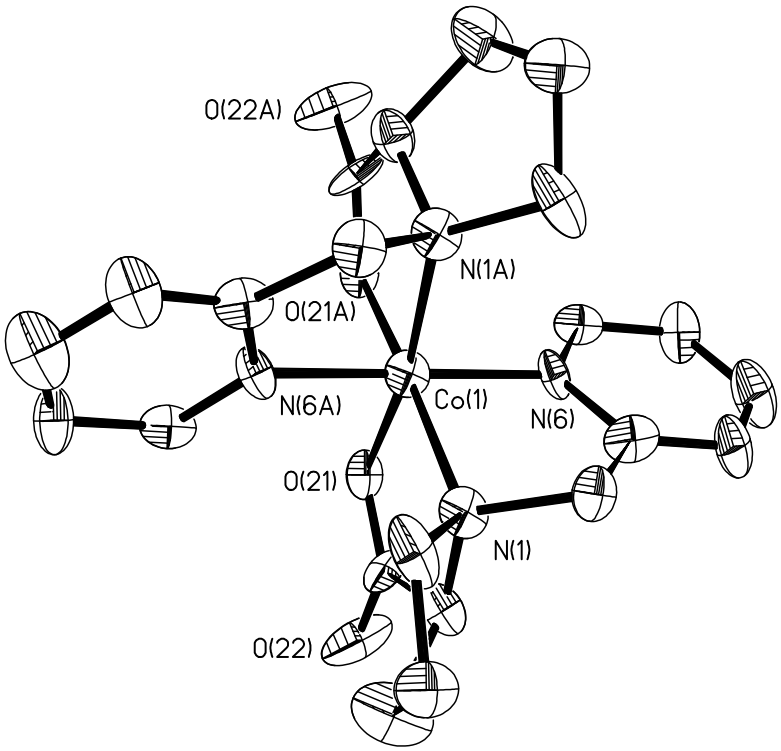


Figure 5.20: A perspective view of the cobalt complex 89. Hydrogen atoms, the bromide counter ion and the water molecule are omitted for clarity. Selected bond lengths (Å) and angles (°): Co(1)-N(1) 2.028(8), Co(1)-N(6) 1.964(7), Co(1)-O(21) 1.895(6), N(1)-Co(1)-N(6) 83.6(3), N(1)-Co(1)-O(21) 85.0(3), N(1)-Co(1)-N(1A) 105.9(4), N(1)-Co(1)-N(6A) 94.0(3), N(1)-Co(1)-O(21A) 168.7(3), N(6)-Co(1)-O(21) 90.2(3), N(6)-Co(1)-N(6A) 176.0(4), N(6)-Co(1)-O(21A) 92.7(3), O(21)-Co(1)-O(21A) 84.3(4).

mounted for preliminary X-ray examination before settling on a very narrow crystal (dimensions 0.44 x 0.09 x 0.04 mm^3) to try and avoid twinning. Despite these precautions the structure was still of low quality.

Structure of 89

Complex **89** crystallizes in tetragonal space group $P4_22_12$ as a 2:1 ligand:metal complex. The asymmetric unit consists of a cobalt atom, located on the two-fold rotation axis, coordinated to a deprotonated ligand through the pyridine nitrogen, amine nitrogen and a carboxylate oxygen in a facial arrangement. The coordination sphere is completed by a symmetry equivalent ligand generated by the two-fold rotation axis (see Figure 5.20). The remainder of the asymmetric unit consists of a half-occupied bromide anion and a quarter-occupied water molecule. There are no notable interactions between adjacent complexes, however they do stack in columns along the *z*-axis, with channels between the columns occupied by the bromide anions and water molecules (see Figure 5.21).

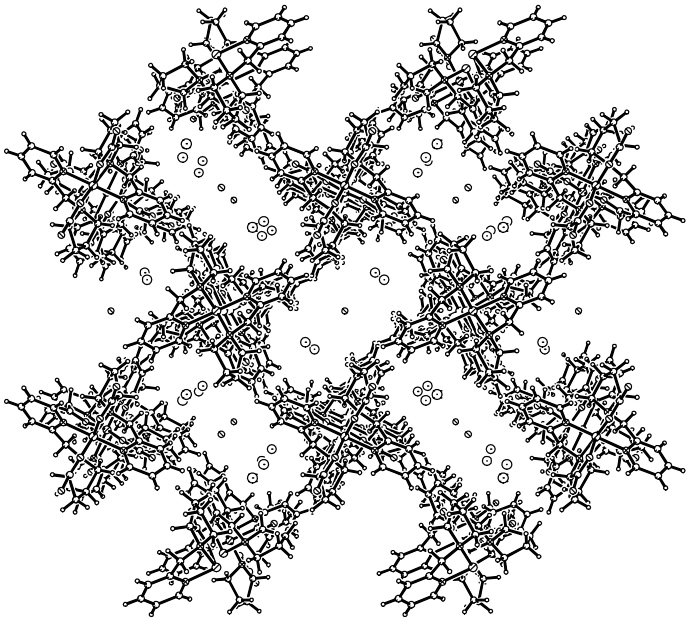


Figure 5.21: A packing diagram of complex 89 showing the bromide anions and water solvate molecules occupying channels between the stacks of complexes.

5.3 Comparison of the Complexes

5.3.1 Complexes of Thiazolidine-based Ligands

The most obvious place to start when comparing these complexes is the metal centres themselves. When the complexes are overlaid, fitting the central metal atom and the three donor atoms, it becomes obvious that the complexes are very similar (see figures 5.22 and 5.23). Unsurprisingly the geometry of the ligand is constrained by the coordination to the metal centre, and as the cobalt and nickel centres are very similar in size and arrangement of donors, there is little difference between the five complexes. The largest variation is in the thiazolidine ring, with differences in the sulfur position visible. This is not a particularly important feature; some of the complexes exhibit disorder in the thiazolidine ring, and not all disorder components were included in this comparison. This reflects a small amount of flexibility in the thiazolidine ring.

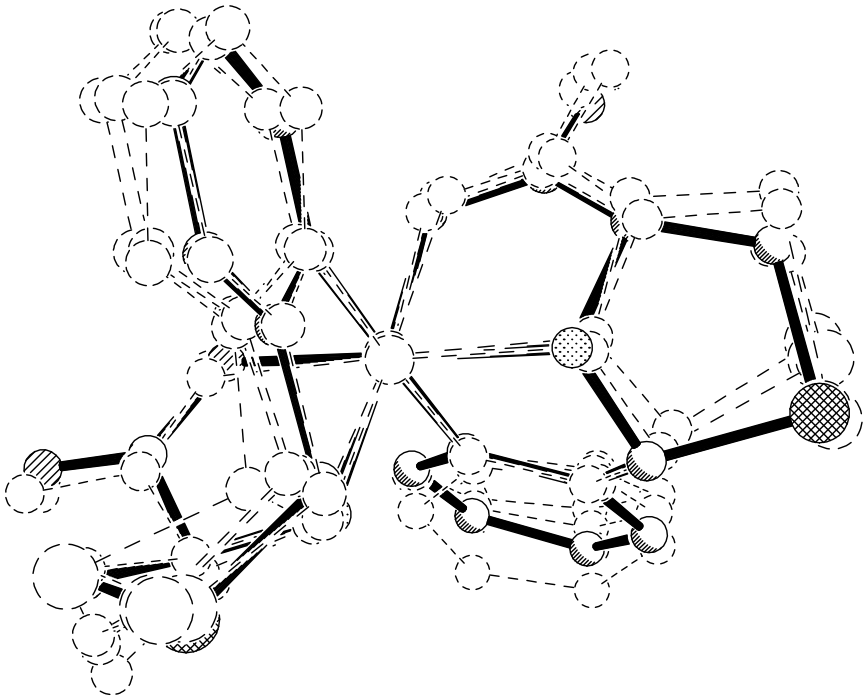


Figure 5.22: An overlay diagram of the five complexes of ligand 75.

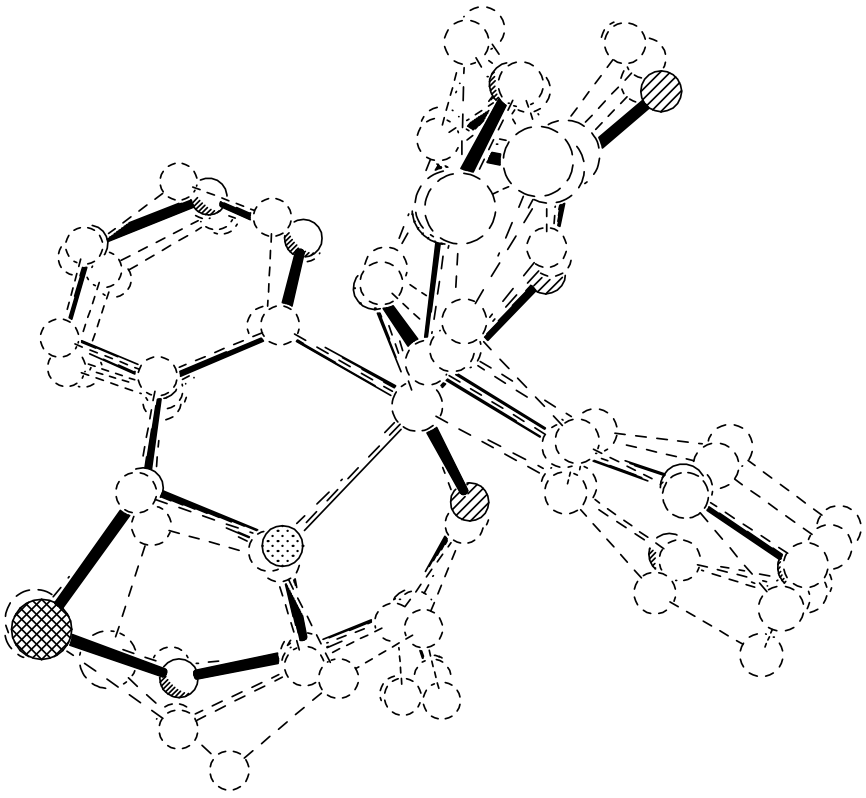


Figure 5.23: A diagram showing the other side of the five overlaid complexes of ligand 75.

When the 10 ligands are themselves directly compared (see Figure 5.24), they are all relatively similar, as would be expected from the overlay of the complexes. The geometry of the ligands is enforced by coordination to the metal centre. In the diagram there appears to be a larger variation in the positions of the pyridine ring and carboxylate group. This is caused by, in this case, fitting the centre thiazolidine ring. This ring, as noted above, has a flexible backbone, and in some cases disorder, so fitting this ring exaggerates the variations of the pyridine and carboxylate groups.

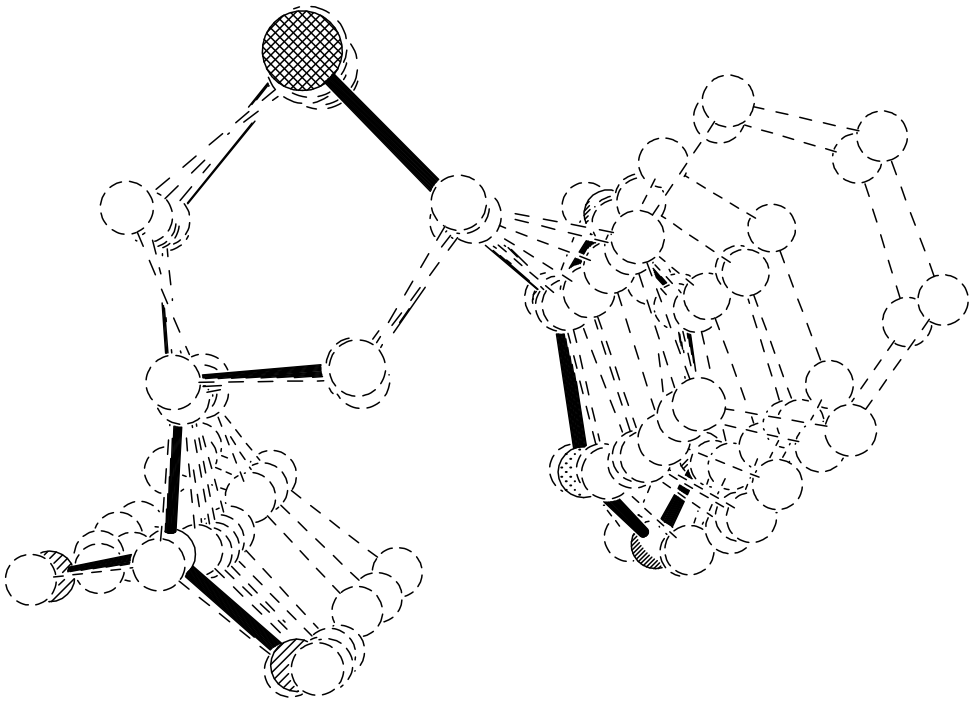


Figure 5.24: An overlay diagram comparing the 10 ligands present amongst the structures.

The hydrogen bonding networks of the different structures are not directly comparable. The networks are influenced by the anions and water molecules present in the structures, and as all have different amounts of these species, none are directly comparable. The complexes themselves have as many as six possible hydrogen bond acceptors, as well as two hydrogen bond donors, which gives them a large amount of flexibility for forming hydrogen bonds. This factor combined with large variation in the other species present leads to a variety of hydrogen bonding networks.

5.3.2 Complexes of N-(picolinamide)-alanine-based Ligands

Comparison of the four different ligands from complexes **87** and **88** shows that the head region of the ligands, which coordinates to the metal centre is, unsurprisingly, almost identical throughout the complexes. The tail region of the

ligands, which are not coordinated, show much more variation. This is unsurprising; the conformation of the tail regions is affected by the steric environment surrounding the complex, rather than coordination to the metal centre, which influences the conformation of the head section (see Figure 5.25). The complexes cannot be compared with respect to the extended structure: not only does different geometry around the metal centre significantly affect the directions in which supramolecular interaction can occur, but one complex has an additional species present, while the other exist as a discrete complex.

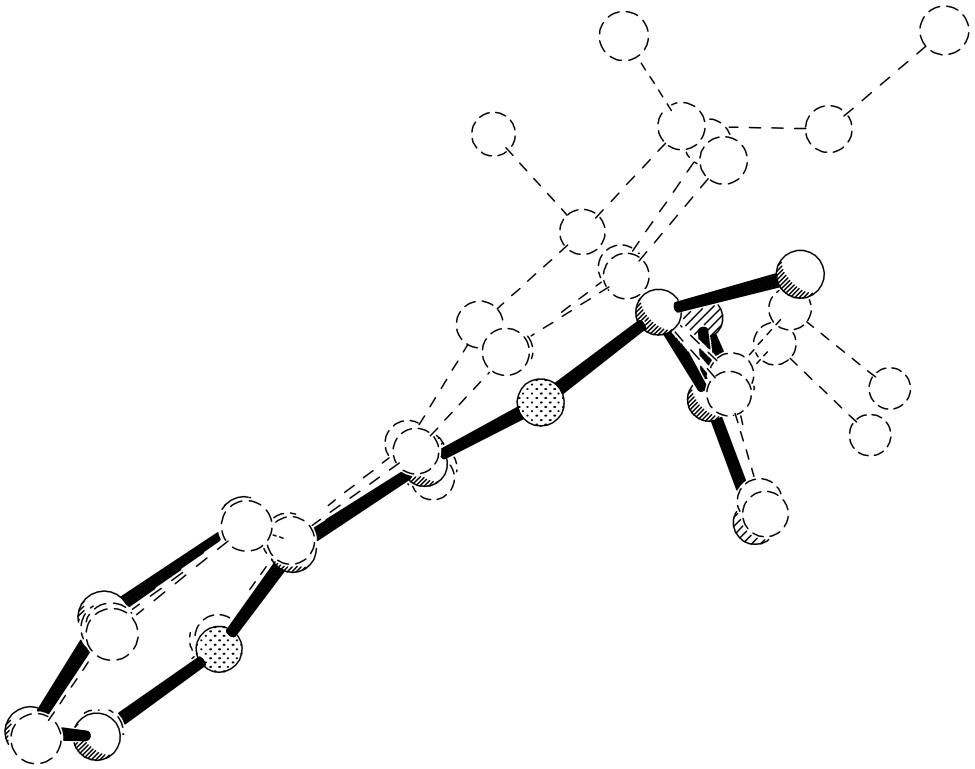


Figure 5.25: A diagram showing the different conformations of the tail units of the four different ligands present in complexes 87 and 88.

5.4 Summary

This chapter has described the coordination and supramolecular chemistry of a range of ligands synthesized from amino acids. A range of substituted thiazolidine-based ligands were synthesized (see Chapter 4), however only complexes of **75** were successfully crystallized and reported here. Two complexes of ligand **72** are also reported here. Although **72** was a precursor to **70**, no complexes of this ligand were successfully crystallized. Finally a single cobalt complex of ligand **65** was reported. Interestingly this series (see Section 4.2) resulted in the most isolated ligands, but these ligands led to only a single crystalline complex.

The five thiazolidine complexes reported in this chapter all have an almost identical coordination geometry around the metal centre. A consequence of this is that the relative conformations of the thiazolidine ligands are all very similar. The variation in conformations is due to the central thiazolidine ring; the sulfur-carbon backside of the ring has some flexibility. The supramolecular chemistry between the complexes in this series is extremely varied, and largely dependant on the ancillary species present in the structures.

The two complexes of ligand **72** reported in this chapter are relatively different. The two different metal centre geometries mean the complexes can not be directly compared. Comparison of the conformation of the ligands reveals that the coordinated head of the molecules are all very similar, while the non-coordinated tails of the molecules show considerable variance. This is unsurprising, as steric effects and supramolecular effects are largely responsible for these conformations, and they differ between the two complexes.

The complex of ligand **65** cannot be directly compared to any other complexes. It is interesting to note the relative similarity of complex **89** to the thiazolidine complexes previously examined in this chapter.

Conclusions

Conclusions

This thesis has described the formation of a number of homochiral coordination complexes and supramolecular assemblies. The ligands utilized were from the alkaloid class of compounds, derivatives thereof, or derived from amino acids. A range of metal atoms with a variety of coordination numbers and geometries, as well as steric sizes was used in the formation of complexes. These factors, in combination with other supramolecular interactions led to a range of supramolecular polymeric and network structures, as well as some discrete species.

The reaction of alkaloids with transition metals resulted in the formation of a number of coordination complexes with interesting structural features. Nicotine formed a number of different complexes, acting as either a monodentate ligand through the pyridine nitrogen, or as a bridging bidentate ligand through both pyridine and amine nitrogens. The conformation of the nicotine molecules was found to be similar to earlier work, and was consistent throughout all the complexes. The stable conformation of the nicotine molecule appeared to have an effect on the supramolecular chemistry, which was observed as consistent structural motifs between different complexes appearing. The other alkaloids studied in this thesis, the cinchona alkaloid family, were involved in three complexes; these were all examples of previously known coordination modes of this family of compounds.

The synthesis of new homochiral ligands from alkaloids was an area of major work in this thesis. A wide range of synthetic routes were investigated, with three new ligands synthesized. The reaction of these ligands with a range of metal salts did not result in any complexes being isolated or characterized.

The synthesis of homochiral ligands from amino acids was the other area of organic chemistry investigated in this thesis. These ligands were divided into

three separate areas: amine-based ligands, amide-based ligands and thiazolidine-based ligands. Six potential ligands designed on the first concept were synthesized. These ligands had three to four possible binding sites, and a range of possible coordination modes. Four potential ligands using the second concept were synthesized. The methyl ester forms of these ligands can act as chelating bidentate ligands, while the hydrolysed derivatives have the potential for an additional bridging interaction. The thiazolidine-based ligands were exclusively chelating ligands (with three to five potential donors), but also possessed additional functionality that could readily be involved in hydrogen bonding.

The coordination chemistry of the amino acid-based ligands was investigated in this thesis. From the thiazolidine-based ligands five complexes were prepared. The complexes all had the same coordination geometry around the central metal atom, but different counter ions and solvate molecules resulted in different supramolecular chemistry in all five crystal structures. The amide-based ligands resulted in two complexes, both of the same methyl ester ligand (**72**). The amine-based ligands resulted in only a single crystal structure, in which the ligand (**65**) coordinates in a chelating tridentate fashion.

Hydrogen bonding was important in the extended three-dimensional structure of many of the complexes described in this thesis. These interactions had a range of effects, from being an important link between molecules in a robust supramolecular motif in one series of complexes, to completely defining the supramolecular chemistry in another series of complexes. Other interactions which were less important in defining extended three-dimensional structure were π-stacking and long range copper(II)-donor interactions.

In summary this thesis has described the synthesis of nineteen homochiral ligands. Chiral coordination complexes of some of these ligands, as well as the parent compounds, were prepared. Twenty of these complexes were characterized by X-ray crystallography. These complexes exhibited a range of structural motifs, some of which were robust and observed across a series of complexes.

The ligands prepared in this thesis have potential applications in asymmetric catalysis and materials research, in which their homochiral nature is important. Similarly, the homochiral coordination complexes prepared in this thesis have potential in these areas, with the chiral, directional coordination polymers prepared in Chapter 2 of interest in non-linear optics.

Experimental

Experimental

7.1 General Experimental

NMR spectra were recorded on Varian Unity 300 or Varian INOVA 500 spectrometers at 23 °C with a 3 mm probe and operating at 300 and 500 MHz for ^{1}H spectra, respectively, and at 75 MHz for ^{13}C spectra (Unity 300 only). ^{1}H-NMR spectra recorded in $CDCl_3$ were referenced to the internal standard Me_4Si, while other solvents were referenced to residual solvent signal. ^{13}C-NMR spectra recorded in $CDCl_3$ were referenced against the solvents signal at 77.0 ppm. When required ^{1}H:^{1}H-COSY, 1-D TOCSY, HSQC and CIGAR experiments were performed using the standard pulse sequences available with the Varian INOVA 500 system. Unless otherwise stated the value of the chemical shift is given to the centre of the multiplet.

Electron Impact (EI) mass spectra were recorded using a Kratos MS80FRA mass spectrometer with a Mach 3 data system. Spectra were obtained at 70 eV with a source temperature of 250 °C. Electrospray mass spectra were recorded using a Micromass LCT TOF mass spectrometer, with the probe operating at 3200 V and a cone voltage of 30 V. Samples were dissolved in 1:1 acetonitrile:water, and spectra acquired using source and desolvation temperatures of 80 and 150 °C, respectively.

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. The Campbell microanalytical laboratory, University of Otago, Dunedin, performed elemental analyses.

Unless otherwise stated, reagents were obtained from commercial sources and used as received. Solvents were purified by standard literature procedures.

7.2 Chapter 2 Experimental

1

Cobalt(II) acetate tetrahydrate (100 mg, 0.4 mmol) and ammonium thiocyanate (122 mg, 1.6 mmol) were dissolved in water (2 mL) to give a red solution. After addition of a solution of nicotine in ethanol (2 mL, 0.4 M) the solution went purple. Slow evaporation of the solution provided red crystals suitable for X-ray crystallography. Yield 217 mg (88 %). M.p. 196-198 °C. Anal. Found: C, 46.45; H, 4.83; N, 18.23. Calc for $C_{24}H_{30}CoN_8S_4$: C, 46.66; H, 4.89; N, 18.14. IR (KBr mull): 2957, 2721, 2081, 1603, 1454, 1402, 1007, 916, 810, 704, 640 cm^{-1}. UV-vis 196 nm (62615 $M^{-1}cm^{-1}$), 327 nm (7586 $M^{-1}cm^{-1}$), 624 nm (1705 $M^{-1}cm^{-1}$).

2 & 7

Hexa(aqua)nickel(II) perchlorate (146 mg, 0.4 mmol) was dissolved in water (2 mL), then nicotine in ethanol solution (2 mL, 0.4 M) followed by sodium thiocyanate in aqueous solution (5 mL, 0.4 M) was added. On addition of the thiocyanate solution a pale blue precipitate formed. After standing over the weekend two different crystalline products had formed, pale blue crystals and purple crystals, both of which were suitable for X-ray crystallography. Purple crystals: Yield 62 mg (18 %). M.p. 243-248 °C. Anal. Found: C, 58.33; H, 6.44; N, 16.44. Calc for $C_{42}H_{56}N_{10}NiS_2.1½H_2O$: C, 59.29; H, 6.99; N, 16.46. IR (KBr mull): 2968, 2941, 2777, 2077, 1603, 1433, 1317, 1111, 1045, 905, 812, 777, 644, 629 cm^{-1}.

An alternative synthesis of only the pale blue crystals involved dissolving nickel(II) acetate tetrahydrate (50 mg, 0.2 mmol) and ammonium thiocyanate (61 mg, 0.8 mmol) in 1:1 ethanol/water (2 mL) and adding a solution of nicotine in ethanol (1 mL, 0.4 M). Blue block-shaped crystals, suitable for X-ray crystallography, formed overnight. Yield 242 mg (98 %). M.p. 270-273 °C. Anal. Found: C, 46.70; H, 4.76; N, 18.22. Calc for $C_{24}H_{30}N_8NiS_4$: C, 46.68; H, 4.90; N, 18.15. IR (KBr mull): 2957, 2723, 2091, 1605, 1454, 1402, 1209, 810, 704, 644 cm^{-1}.

3

Tetrakis(acetonitrile)copper(I) tetrafluoroborate (126 mg, 0.4 mmol) was dissolved in acetonitrile (2 mL) and a solution of nicotine (130 mg, 0.8 mmol) dissolved in 40% calcium thiocyanate solution (1 mL) was added. A white precipitate formed, which immediately redissolved. Slow evaporation of the solution provided green crystals suitable for X-ray crystallography. An alternative preparation directly from copper(II) was also performed: Copper(II) acetate hydrate (40 mg, 0.2 mmol) and ammonium thiocyanate (61 mg, 0.8 mmol) were dissolved in 1:1 ethanol/water (2 mL). Upon addition of a solution of nicotine in 1:1 water/ethanol (1 mL, 0.4 M) the solution went green and a brown suspension formed. Upon standing for a long period green crystals suitable for X-ray crystallography formed. Yield 42 mg (29 %). M.p. 251-254 °C. Anal. Found: C, 45.00; H, 4.96; N, 18.81. Calc for $C_{24}H_{30}CuN_8S_4.7/4(H_2O).3/2(MeCN)$: C, 45.33; H, 5.35; N, 18.60. IR (KBr mull): 3115, 2962, 2722, 2065, 1608, 1457, 1400, 1208, 1097, 1009, 963, 900, 810, 701, 653 cm^{-1}.

4

Cadmium(II) acetate dihydrate (107 mg, 0.4 mmol) and ammonium thiocyanate (122 mg, 1.6 mmol) were dissolved in 1:1 water/ethanol and a solution of nicotine in ethanol was added (1 mL, 0.4 M). Slow evaporation of the solution provided crystals suitable for X-ray crystallography. Yield 101 mg (75 %). M.p. 201.5-202 °C. Anal. Found: C, 42.63; H, 4.48; N, 16.30. Calc for $C_{24}H_{30}CdN_8S_4$: C, 42.94; H, 4.50; N, 16.30.

5

Iron(II) sulphate (61 mg, 0.4 mmol) and ammonium thiocyanate (61 mg, 0.8 mmol) were dissolved in deoxygenated water under N_2. A solution of nicotine in water (1 mL, 0.4 M) was deoxygenated and then added to the iron(II) solution. An immediate green precipitate formed, as well as a number of small orange crystals on the side of the vial. These crystals were suitable for X-ray crystallography, although only identification of the compound was possible, as

crystal quality was too low for complete refinement. Unfortunately these crystals were too unstable in air for any other analyses to be carried out.

6

Freshly recrystallized manganese(II) acetate tetrahydrate (49 mg, 0.2 mmol) and ammonium thiocyanate (61 mg, 0.8 mmol) were dissolved in deoxygenated water (2 mL) under N_2. A solution of nicotine in ethanol (1 mL, 0.4 M) deoxygenated with N_2 was added. Slow evaporation of the solvent under N_2 provided crystals suitable for X-ray crystallography, although only identification of the compound was possible, as crystal quality was too low for complete refinement. Complex **6** was too unstable in air for further analyses to be carried out.

8

A solution of nicotine in acetonitrile (0.4 M, 1 mL) was added to a solution of silver(I) nitrate (66 mg, 0.4 mmol) in acetonitrile (1 mL). A crystalline product was obtained by the diffusion of ether into the solution. Yield 74 mg (56 %). M.p. 149-151 °C (dec.). Anal. Found: C, 35.98; H, 4.29; N, 12.91. Calc for $C_{10}H_{14}AgN_3O_3$: C, 36.17; H, 4.25; N, 12.65. ^{1}H-NMR (500 MHz, CD_3CN): δ 8.70 (1H, d, H2), 8.55 (1H, dd, H6), 7.99 (1H, dt, H5), 7.56 (1H, dd, H4), 3.37-3.41 (1H, m, H7), 3.31 (1H, t, H9a), 2.45-2.50 (1H, m, H9b), 2.33-2.39 (1H, m, H11a), 2.32 (s, 3H, NCH_3), 2.05-2.11 (1H, m, H10a), 1.94-2.00 (1H, m, H10b), 1.87-1.91 (1H, m, H11b). ES-MS: Found M^+ 600.0, $[Ag_2(nicotine)_2(NO_3)]^+$ requires M^+ 600.0; found M^+ 431.1, $[Ag(nicotine)_2]^+$ requires M^+ 431.1; found M^+ 310.0, $[Ag(nicotine)(CH_3CN)]^+$ requires M^+ 310.0. IR (KBr mull): 2967, 2871, 2797, 2398, 1753, 1597, 1388, 899, 807, 714 cm^{-1}.

9

A solution of nicotine in acetonitrile (0.4 M, 3 mL) was added to silver(I) nitrate (66 mg, 0.4 mmol) dissolved in acetonitrile (4 mL). A crystalline product was obtained by the diffusion ofdiethyl ether into the solution. Yield 146 mg (74 %).

M.p. 141-142 ºC (dec.). Anal. Found: C, 48.78; H, 5.70; N, 14.27. Calc for $C_{20}H_{28}AgN_5O_3$: C, 48.59; H, 5.71; N, 14.17). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.69 (1H, s, H2), 8.54 (1H, d, H6), 7.82-7.85 (1H, m, H5), 7.36-7.40 (1H, m, H4), 3.48 (1H, s, H7), 3.35 (1H, t, H9a), 3.16 (1H, t, H9b), 2.20-2.42 (1H, m, H11a), 2.26 (3H, s, NCH_3), 1.97-2.01 (1H, m, H10a), 1.81-1.86 (2H, m, H10b, H11b). IR (KBr mull): 2976, 2770, 1762, 1576, 1390, 1035, 903, 807, 716 cm^{-1}.

10

A solution of nicotine in acetonitrile (0.4 M, 1 mL) was added to silver(I) tetrafluoroborate (78 mg, 0.4 mmol) dissolved in acetonitrile (2 mL). A crystalline product was obtained by the diffusion of ethyl acetate into the solution. Yield 126 mg (72 %). M.p. 135-140 °C (dec.). Anal. Found: C, 33.66; H, 4.28; N, 7.81. Calc for $C_{10}H_{14}BF_4N_2Ag$: C, 33.65; H, 3.95; N, 7.85. IR (KBr mull): 2943, 2781, 1578, 1427, 1315, 1042(br), 905, 808, 718, 534, 523 cm^{-1}.

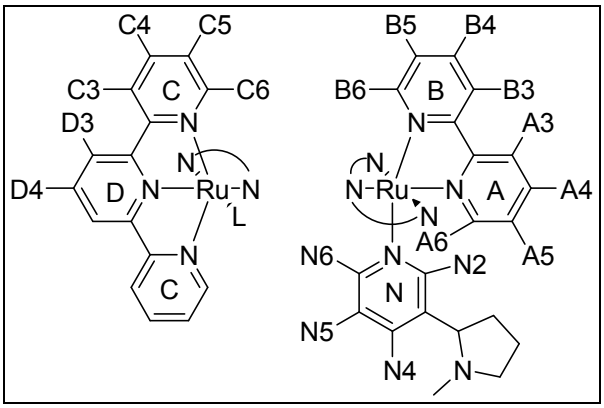
12

Bis(2,2'-bipyridine)dichlororuthenium(II) (30.0 mg, 0.062 mmol) and nicotine (1 drop) were refluxed for two days in 3:1 ethanol:water (8 mL). The solution was cooled to room temperature and reduced *in vacuo*. A saturated aqueous solution of ammonium hexafluorophosphate was added until no further precipitation was observed. The fine red solid product was removed by filtration and washed with water (3 x 2 mL) and air dried. Yield 26 mg (55.5%). Anal. Found: C, 45.08; H, 3.77; N, 10.52. Calc for $C_{30}H_{30}ClF_6N_{12}PRu.2½H_2O$: C, 44.98; H, 4.40; N, 10.21.

13

Complex **13** was synthesized by adapting the method of Calvert *et al*.[42] (2,2'-Bipyridine)chloro(2,2':6',2"-terpyridine)ruthenium(II) hexafluorophosphate (25 mg, 0.04 mol) and nicotine (81 mg, 0.5 mmol) were dissolved in 1:1 ethanol:water (12.5 mL). The solution was refluxed overnight with stirring. The solution was cooled, and reduced to half-volume *in vacuo*, and a solution of

saturated aqueous ammonium hexafluorophosphate was added until no further precipitation was observed. The red-brown product was removed by filtration and washed with water (3 x 2 mL). This product was purified by column chromatography on alumina eluting with 2:1 toluene:acetonitrile. Yield. 20 mg (53 %). ^{1}H-NMR (500 MHz, CD_3CN): δ 8.76 (d, 1H, A6), 8.74 (d, 1H, A3), 8.57 (dd, 1H, D3), 8.48-8.50 (m, 3H, B3 (1H) & C3 (2H)), 8.37 (t, 1H, A4), 8.25 (t, 1H, D4), 8.07-8.10 (m, 2H, C4), 7.86-7.90 (m, 4H, A5 (1H) & B4 (1H) & C6 (2H)), 7.78 (s, 1H, N2), 7.72 (d, 1H, N6), 7.57 (d, 1H, N4), 7.43-7.49 (m, 2H, C5), 7.37 (d, 1H, B6), 7.18 (dd, 1H, N5), 7.14 (t, 1H, B5). See diagram below for ring assignments. Pyrrolidine protons of nicotine were unassigned. C ring protons are not truly equivalent, which is observed as a broadening of those signals in the spectra. Anal. Found: C, 43.77; H, 4.00; N, 10.71. Calc for $C_{35}H_{33}F_{12}N_7P_2Ru.H_2O$: C, 43.76; H, 3.67; N, 10.21.



14

Hexa(aqua)copper(II) perchlorate (74 mg, 0.2 mmol) and nicotine (39 mg, 0.24 mmol) were dissolved in methanol (3 mL). A solution of 2,2',6',2''-terpyridine (28 mg, 0.12 mmol) dissolved in methanol (4 mL) was added dropwise with stirring. A purple-blue solid formed in the blue solution. The solid was removed by filtration, and recrystallisation from hot methanol was unsuccessful. Crystals of the desired product, suitable for X-ray crystallography, were obtained by slow diffusion of diethyl ether vapour into the filtrate.

15

Copper(II) chloride (10 mg, 0.075 mmol) and quinine (32 mg, 1 mmol) were dissolved in 2:1 acetonitrile:methanol (5 mL). Crystals suitable for X-ray crystallography formed on standing overnight. Yield 29 mg (80 %). M.p. 166-168 °C. Anal. Found: C, 54.07; H, 5.43; N, 8.47. Calc for $C_{40}H_{46}Cl_2Cu_2N_4O_4.(CH_3CN)_2(H_2O)_2$: C, 54.88; H, 5.86; N, 8.73.

16

Copper(II) bromide (14 mg, 0.065 mmol) and quinine (32 mg, 1 mmol) were dissolved in 2:1 acetonitrile:methanol (5 mL). Upon standing overnight a green powder formed, which redissolved when the solution was heated. The solution was allowed to stand overnight again, and green crystals suitable for X-ray crystallography formed. Yield 22 mg (67 %). M.p. 154-157 °C. Anal. Found: C, 52.13; H, 5.09; N, 8.26. Calc for $C_{40}H_{46}Cl_2Br_2N_4O_4.(CH_3CN)_2$: C, 52.02; H, 5.16; N, 8.27.

17

Hexa(aqua)cobalt(II) chloride (118 mg, 0.5 mmol) was dissolved in ethanol (2 mL) and a solution of quinine (162 mg, 0.5 mmol) in ethanol (2 mL) was added. A light blue precipitate formed immediately, and small crystals formed over a period of three hours. These crystals were left overnight, after which they were of sufficient quality for preliminary X-ray crystallographic investigation. This investigation revealed the structure to be related to previously reported compounds; this fact in conjunction with the low quality of the crystals led to no further analysis being attempted.

7.3 Chapter 3 Experimental

25

Compound **25** was synthesized from nicotine by the method of Taylor[55] with yields similar to those originally reported (~70 %).

22

Compound **22** was synthesized by the method of Schmidt and Neitemeier[44] in variable yields (10-60 %).

20 from 22

The synthesis of **20** from **22** was attempted using the method of Schmidt and Neitemeier. The reaction was performed both in the presence and absence of diisopropylamine, as reported, by both syntheses resulted in none of the desired **20**.

23

Compound **23** was synthesized using the method of Rolf[54] in high yields (>90 %).

27

Compound **27** was synthesized by adapting the synthesis of **25**. Cotinine (176 mg, 1 mmol) was dissolved in acetic acid (5 mL) and 30% hydrogen peroxide (1 mL) was added. The resulting solution was stirred overnight at 60 °C. The solvent was removed *in vacuo* to provide the product as a pale yellow oil. Yield 190 mg (99 %).

Reaction of 27 with phosphorus oxychloride

Compound **27** (19 mg, 0.1 mmol) was mixed with freshly distilled phosphorus oxychloride (2.5 mL). The solution was refluxed overnight with vigorous stirring under a nitrogen atmosphere. The solution was cooled, and carefully poured onto ice (5 mL). The resulting solution was neutralized with solid sodium bicarbonate then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis

of the product by 1H-NMR revealed that the pyridine ring had not been substituted and that the five-membered ring had undergone an unidentified transformation.

Reaction of 23 with phosphorus oxychloride

Compound **23** (17 mg, 0.1 mmol) was mixed with freshly distilled phosphorus oxychloride (2.5 mL). The solution was refluxed overnight with vigorous stirring under a nitrogen atmosphere. The solution was cooled, and carefully poured onto ice (5 mL). The resulting solution was neutralized with solid sodium bicarbonate then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the product by 1H-NMR revealed that the pyridine ring had not been substituted and that the five-membered ring had undergone an unidentified transformation.

Reaction of 25 with phosphorus oxychloride

Compound **25** (19 mg, 0.1 mmol) was mixed with freshly distilled phosphorus oxychloride (2.5 mL). The solution was refluxed overnight with vigorous stirring under a nitrogen atmosphere. The solution was cooled, and carefully poured onto ice (5 mL). The resulting solution was neutralized with solid sodium bicarbonate then extracted with dichloromethane (3 x10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. No product was present

28

Compound **28** was synthesized by the method of Taylor[55] in quantitative yield (>99 %).

Reaction of 28 with phosphorus oxychloride

Compound **28** (19 mg, 0.1 mmol) was mixed with freshly distilled phosphorus oxychloride (2.5 mL). The solution was refluxed overnight with vigorous stirring under a nitrogen atmosphere. The solution was cooled, and carefully poured onto ice (5 mL). The resulting solution was neutralized with solid sodium bicarbonate then extracted with dichloromethane (3 x 10 mL). The combined

organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*, but no product was present. Attempted extraction with common laboratory solvents also failed to provide any product.

Reaction of 22 with acetic anhydride

Compound **22** (18 mg, 0.1 mmol) was dissolved in acetic anhydride (2.5 mL), and the solution refluxed overnight with stirring under a nitrogen atmosphere. The solution was cooled and added to water (10 mL). The solution was neutralized with solid sodium carbonate and extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide a pale brown oil. Analysis of the product by ^{1}H-NMR revealed only starting material.

Reaction of 28 with acetic anhydride

Compound **28** (18 mg, 0.1 mmol) was dissolved in acetic anhydride (2.5 mL), and the solution refluxed overnight with stirring under a nitrogen atmosphere. The solution was cooled and added to water (10 mL). The solution was neutralized with solid sodium carbonate and extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide a pale brown oil. Analysis of the product by ^{1}H-NMR revealed only starting material.

Reaction of 27 with acetic anhydride

Compound **27** (18 mg, 0.1 mmol) was mixed with acetic anhydride (2.5 mL). The solution was refluxed overnight with vigorous stirring under a nitrogen atmosphere. The solution was cooled, and carefully poured onto ice (5 mL). The resulting solution was neutralized with solid sodium bicarbonate then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the product by ^{1}H-NMR revealed that the pyridine ring had not been substituted and that the five-membered ring had undergone an unidentified transformation.

Reaction of 23 with acetic anhydride

Compound **23**(19 mg, 0.1 mmol) was mixed with acetic anhydride (2.5 mL). The solution was refluxed overnight with vigorous stirring under a nitrogen atmosphere. The solution was cooled, and carefully poured onto ice (5 mL). The resulting solution was neutralized with solid sodium bicarbonate then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the product by ^{1}H-NMR revealed that the pyridine ring had not been substituted and that the five-membered ring had undergone an unidentified transformation.

Attempted synthesis of 6-(triethylammonium)nicotine acetate

22 (178 mg, 1 mmol) was dissolved in dry dichloromethane (10 mL) under an argon atmosphere. The solution was cooled to -25 °C and dry, freshly distilled triethylamine (1.4 mL, 10 mmol) was added dropwise. A solution of acetyl chloride (156 mg, 2 mmol) in dry dichloromethane (2 mL) was added dropwise over the course of 30 minutes, during which time the solution was maintained below -15 °C. The solution was maintained at -15 °C for a further 90 minutes, after which it was allowed to come to room temperature and stirred for a further 3 hours. The solution was then treated with diethyl ether (20 mL) and the solid removed by filtration. The filtrate was concentrated *in vacuo* to provide a brown oil. Analysis of this revealed only starting material present.

30

30 was synthesized by the method of Seeman and Whidby[35] in quantitative yield (>99 %).

29

29 was synthesized using the method of Acheson *et al.*[47] Alternative purification is as follows. Following extraction of the reaction medium with chloroform, the organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was dissolved in the minimum amount of water and added to a Sephadex column. The column was eluted with water, and the collected eluent was reduced *in vacuo* to provide the desired product as a brown oil. Subsequent elution of the column with 1 M sodium chloride solution provided a solution

containing the starting material, which could be recovered by reducing the solution *in vacuo* and extracting the solid with chloroform.

20 from 29

29 (192 mg, 1 mmol) and phosphorus pentachloride (312 mg, 1.5 mmol) were placed in a dry round-bottomed flask. Freshly distilled phosphorus oxychloride (5 mL) was added and the solution was refluxed overnight with vigorous stirring. The solution was cooled, and most of the phosphorus oxychloride was removed by distillation under reduced pressure. The residue was treated with ice water (10 mL), then neutralized with solid sodium carbonate. The neutral solution was then extracted with ethyl acetate (3 x 10 mL), and the combined organic phases were dried (Na_2SO_4) and reduced *in vacuo*. The resultant oil was purified by gradient column chromatography on silica, eluting with petroleum ether/chloroform. The desired product was obtained as a or pale brown oil. Yield 31 mg (16 %). Spectroscopic data for the product matched literature values.[47]

Attempted demethylation of 29 using Pd/C

Compound **29** (38 mg, 0.2 mmol) and palladium on carbon (20 mg) were placed in a dry flask with a magnetic flea. The flask was subsequently evacuated and flushed with argon gas carefully several times. After the final evacuation dry dichloromethane (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After washing the plug with further dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only the starting material.

Attempted demethylation of 29 using Pearlman's Catalyst

Compound **29** (38 mg, 0.2 mmol) and Pearlman's Catalyst (20 mg) were placed in a dry flask with a magnetic flea. The flask was subsequently evacuated and flushed with argon gas carefully several times. After the final evacuation dry dichloromethane (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After

washing the plug with further dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only the starting material.

Demethylation of 30 using boron tribromide

Compound **30** (38 mg, 0.2 mmol) was placed in a dry flask with a magnetic flea. Boron tribromide (5 mL) was added, and the solution was stirred overnight under argon. The solution was then cooled in an ice bath, and water was added carefully dropwise. After no further reaction was observed the resulting solution was neutralized with solid sodium bicarbonate. The solution was then extracted with dichloromethane (3 x 10 mL), and the organic phase was dried (Na_2SO_4) and reduced *in vacuo*. The residue was analysed by ^{1}H-NMR, and revealed only starting material.

Reaction of 29 with phosphorus tribromide

Compound **29** (192 mg, 1 mmol) was dissolved in dry chloroform (15 mL). Phosphorus tribromide (1 mL) was added and the resulting solution was stirred overnight. The solvent was removed *in vacuo* and the residue dissolved in water (10 mL). The solution was neutralized with solid sodium carbonate and extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was analysed by ^{1}H-NMR, and revealed only starting material. The reaction was repeated in the absence of chloroform using 2 mL of phosphorus tribromide with the same result.

Attempted synthesis of 32 from 29 using the method of Kato and co-workers[57]

Compound **29** (192 mg, 1 mmol), phosphorus pentoxide (355 mg, 2.5 mmol) and tetraethylammonium bromide (184 mg, 1.2 mmol) were dissolved in toluene (25 mL) and the solution was stirred at 95 °C for 1.5 hours. After cooling to room temperature the upper organic layer was removed. The lower layer was extracted with toluene (10 mL). The combined organic phases were washed with aqueous sodium bicarbonate solution, brine, then dried (Na_2SO_4). The solvent

was removed *in vacuo*, after which analysis by ^{1}H-NMR revealed only the starting material.

Attempted synthesis of 32 from 29 using the method of Sugimoto and co-workers[58]

Freshly recrystallized N-bromosuccinimide (890 mg, 5 mmol) was added to a solution of triphenyl phosphine (1.31 g, 5 mmol) in absolute dioxane (50 mL) and then stirred for 30 minutes. A solution of **29** (192 mg, 1 mmol) in dioxane (10 mL) was added and the solution refluxed overnight. The solvent was removed *in vacuo*, dissolved in dichloromethane (50 mL), and basified with triethylamine. Chromatography on silica gel eluting with 1:1 petroleum ether:dichloromethane removed the reagents and by-products. Analysis of the residue by ^{1}H-NMR revealed only starting material.

33

Nicotine (2 g, 12.3 mmol) was added carefully to 13 mL of glacial acetic acid and cooled to 0 °C. Benzyl bromide (4.21 g, 24.6 mmol) was added in a single portion. The solution was swirled to mix and then left to stand for 3 days. The solvent was then removed *in vacuo* and 5 mL water was added. The solution was neutralized with excess solid sodium carbonate and extracted with dichloromethane (3 x 30 mL). The organic phase was dried (Na_2SO_4) and the solvent then removed *in vacuo*. The residue was dissolved in 100:1 $CHCl_3$:MeOH and adsorbed onto an alumina column. Elution with $CHCl_3$ provided a forerun which proved to be unreacted benzyl bromide, followed by a band which was identified as a mixture of the desired product and starting materials. Elution with 100:1 $CHCl_3$:MeOH provided a band which was only the desired product, as a dark brown oil. Elution with 1:1 $CHCl_3$:MeOH gave a final band which consisted of a mixture of the desired product and starting materials. The second band was used and no further purification was attempted. Yield 1.72 g (42 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.55 (1H, d, H6), 9.36 (1H, s, H2), 8.38 (1H, d, H4), 7.97 (1H, dd, H5), 7.66-7.68 (2H, m, H3'), 7.36-7.39 (3H, m, H4', H5'), 6.29 (2H, dd, H1'), 3.51-3.54 (1H, m, H9a), 3.21 (1H, ddd, H7), 2.36-2.44

(2H, m, H9b, H11a), 2.18 (3H, s, NCH_3), 1.81-1.93 (2H, m, H10a, H10b), 1.60-1.67 (1H, m, H11b). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 145.91, 144.05, 143.70, 143.42, 132.94, 129.93, 129.60, 129.50, 128.13, 66.92, 64.32, 56.62, 40.32, 35.49, 23.03. ES-MS: Found M^+ 253.1699, $C_{17}H_{21}N_2^+$ requires M^+ 253.1705. IR (KBr plates): 3422, 3024, 2947, 2361, 2341, 1634, 1456, 1205, 1151, 685 cm^{-1}.

34

33 (1.7 g, 5.1 mmol) was dissolved in water (8 mL). Potassium ferricyanide (3.3 g, 10 mmol) and potassium hydroxide (1.55 g, 27.6 mmol) dissolved in water (13 mL) were added over 30 minutes under argon, keeping the temperature under 15 °C. Ethanol (2 mL) was added to help dissolve the starting material. After one day of stirring at room temperature further potassium ferricyanide (3.3 g, 10 mmol) and potassium hydroxide (1.55 g, 27.6 mmol) dissolved in of water (13 mL) were added and the mixture stirred for a further two days. The solution was filtered and then extracted with dichloromethane (3 x 20 mL). The solvent was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was dissolved in 3:1 water:acetone (50 mL) and run through a short Sephadex column to remove any starting material. The solvent was removed *in vacuo* to provide the pure product as a brown oil. Yield 0.822 g (60 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37 (1H, dd, H4), 7.33 (2H, d, H3'), 7.28-7.29 (3H, m, H4' ,H5'), 7.16 (1H, d, H2), 6.618 (1H, d, H5), 5.13 (2H, dd, H1'), 3.16 (1H, t, H9a), 2.74 (1H, t, H7), 2.21 (1H, dd, H9b), 2.12 (3H, 2, NCH_3), 2.01-2.08 (1H, m, H11a), 1.83-1.90 (1H, m, H10a), 1.71-1.78 (1H, m, H10b), 1.60-1.67 (1H, m, H11b). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 162.61, 139.39, 136.54, 134.97, 128.78, 128.04, 127.86, 127.81, 121.35, 120.89, 67.69, 56.59, 51.91, 40.08, 33.70, 22.24. ES-MS: Found M^+ 269.1653, $[C_{17}H_{20}N_2O.H]^+$ requires M^+ 269.1654. IR (KBr plates): 3425, 3032, 2779, 1665, 1599, 1144, 1043, 835, 698 cm^{-1}.

Reaction of 34 with phosphorus oxychloride

Freshly distilled phosphorus oxychloride (10 mL) was added to compound **34** (26.8 mg, 0.1 mmol). The mixture was stirred vigorously at reflux overnight. After cooling the phosphorus oxychloride was removed by distillation under reduced pressure. The residue was dissolved in ice water (10 mL), neutralized with solid sodium carbonate and extracted with dichloromethane (3 x 10 mL). The

combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only the starting material.

Reaction of 34 with phosphorus tribromide

Compound **34** (268 mg, 1 mmol) was dissolved in dry chloroform (15 mL). Phosphorus tribromide (1 mL) was added and the resulting solution was stirred overnight. The solvent was removed *in vacuo* and the residue dissolved in water (10 mL). The solution was neutralized with solid sodium carbonate and extracted with dichloromethane (3 x 10 mL). The combined organic phases was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was analysed by ^{1}H-NMR, and revealed only starting material. The reaction was repeated in the absence of chloroform using 2 mL of phosphorus tribromide with the same result.

Attempted bromination of 34 using the method of Kato and co-workers[57]

34 (268 mg, 1 mmol), phosphorus pentoxide (355 mg, 2.5 mmol) and tetraethyl ammonium bromide (184 mg, 1.2 mmol) were dissolved in toluene (25 mL) and the solution was stirred at 95 °C for 1.5 hours. After cooling to room temperature the upper organic layer was removed. The lower layer was extracted with toluene (10 mL). The combined organic phases were washed with aqueous sodium bicarbonate solution, brine, then dried (Na_2SO_4). The solvent was removed *in vacuo*, after which analysis by ^{1}H-NMR revealed only the starting material.

Attempted bromination of 34 using the method of Sugimoto and co-workers[58]

Freshly recrystallized N-bromosuccinimide (890 mg, 5 mmol) was added to a solution of triphenylphosphine (1.31 g, 5 mmol) in absolute dioxane (50 mL) and then stirred for 30 minutes. A solution of **34** (268 mg, 1 mmol) in dioxane (10 mL) was added and the solution refluxed overnight. The solvent was removed *in vacuo*, the residue redissolved in dichloromethane (50 mL), and basified with triethylamine. Chromatography on silica gel eluting with 1:1 petroleum

ether:dichloromethane removed the reagents and by-products. Analysis of the residue by ^{1}H-NMR revealed only starting material.

Attempted debenzylation of 34 using boron tribromide

Compound **34** (268 mg, 1 mmol) was stirred with boron tribromide (5 mL) overnight at room temperature. The solution was carefully added to water (25 mL) and the solution neutralized with solid sodium carbonate. The solution was then extracted with dichloromethane (3 x 15 mL). The combine organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only starting material.

Attempted debenzylation of 34 using Pd/C in acetic acid

Compound **34** (54 mg, 0.2 mmol) and palladium on carbon (20 mg) were placed in a dry flask with a magnetic flea. The flask was subsequently evacuated and flushed with argon gas carefully several times. After the final evacuation acetic acid (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After washing the plug with dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only the starting material.

Attempted debenzylation of 34 using Pearlman's Catalyst in acetic acid

Compound **34** (54 mg, 0.2 mmol) and Pearlman's Catalyst (20 mg) were placed in a dry flask with a magnetic flea. The flask was subsequently evacuated and flushed with argon gas carefully several times. After the final evacuation acetic acid (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After washing the plug with dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only the starting material.

Attempted debenzylation of 34 using Pd/C in trifluoroacetic acid

Compound **34** (54 mg, 0.2 mmol) and palladium on carbon (20 mg) were placed in a dry flask with a magnetic flea. The flask was evacuated and flushed with argon gas carefully several times. After the final evacuation trifluoroacetic acid (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After washing the plug with dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only the starting material.

Attempted debenzylation of 34 using Pearlman's Catalyst in trifluoroacetic acid

Compound **34** (54 mg, 0.2 mmol) and Pearlman's Catalyst (20 mg) were placed in a dry flask with a magnetic flea. The flask was evacuated and flushed with argon gas carefully several times. After the final evacuation trifluoroacetic acid (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After washing the plug with dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only the starting material.

Reaction of nicotine with 2-bromoethanol

Nicotine (162 mg, 1 mmol) and 2-bromoethanol (125 mg, 1mmol) were dissolved in acetic acid (5 mL) and the solution stirred overnight. The solution was reduced *in vacuo* and the residue was dissolved in water (10 mL). The resulting solution was neutralized with solid sodium bicarbonate and then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR showed only nicotine.

Reaction of nicotine with chloromethyl methyl ether

Nicotine (162 mg, 1 mmol) and chloromethyl methyl ether (81 mg, 1 mmol) were dissolved in acetic acid (5 mL) and the solution stirred overnight at room temperature. The solution was reduced *in vacuo* and the residue was dissolved

in water (10 mL). The resulting solution was neutralized with solid sodium bicarbonate and then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR showed only nicotine.

Reaction of nicotine with 4-bromobenzyl bromide

Nicotine (162 mg, 1 mmol) and 4-bromobenzyl bromide (250 mg, 1 mmol) were dissolved in acetic acid (5 mL) and the solution stirred overnight at room temperature. The solution was reduced *in vacuo* and the residue was dissolved in water (10 mL). The resulting solution was neutralized with solid sodium bicarbonate and then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR showed only nicotine.

35

Nicotine (162 mg, 1 mmol) and 1-bromomethyl-4-nitrobenzene (216 mg, 1 mmol) were dissolved in acetic acid (5 mL) and the solution was stirred overnight at room temperature. The solution was then reduced *in vacuo* and the residue dissolved in water (10 mL). The resulting solution was neutralized with solid sodium bicarbonate and the extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide **35** as a brown oil.

Attempted synthesis of 37

Compound **37** (189 mg, 0.5 mmol) was dissolved in water (4 mL). Potassium ferricyanide (330 mg, 1 mmol) and potassium hydroxide (168 mg, 3 mmol) dissolved in water (10 mL) were added over 30 minutes under argon, keeping the temperature under 15 °C. Ethanol (2 mL) was added to help dissolve the starting material, which was observed coating the walls of the flask. After one day of stirring at room temperature further potassium ferricyanide (330 mg, 1 mmol) and potassium hydroxide (168 mg, 3 mmol) dissolved in water (10 mL) was added and the mixture stirred for a further two days. The solution was filtered and then extracted with dichloromethane (3 x 10 mL). The reaction vessel

was also rinsed with dichloromethane (10 mL). The solvent was dried (Na_2SO_4) and then removed *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only starting material.

39

Nicotine (162 mg, 1 mmol) and 1-chloromethyl-4-methoxybenzene (157 mg, 1 mmol) were dissolved in acetic acid (5 mL) and the solution was stirred overnight at room temperature. The solution was then reduced *in vacuo* and the residue dissolved in water (10 mL). The resulting solution was neutralized with solid sodium bicarbonate and then extracted with dichloromethane (3 x 10mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide **39** as a brown oil.

40

Nicotine (162 mg, 1 mmol) and 1-bromomethyl-4-methylbenzene (185 mg, 1 mmol) were dissolved in acetic acid (5 mL) and the solution was stirred overnight at room temperature. The solution was then reduced *in vacuo* and the residue dissolved in water (10 mL). The resulting solution was neutralized with solid sodium bicarbonate and the extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent remove *in vacuo* to provide **40** as a brown oil.

Attempted synthesis of 41

39 (160 mg, 0.5 mmol) was dissolved in water (4 mL). Potassium ferricyanide (330 mg, 1 mmol) and potassium hydroxide (168 mg, 3 mmol) dissolved in water (10 mL) were added over 30 minutes under argon, keeping the temperature under 15 °C. Ethanol (2 mL) was added to help dissolve the starting material, which was observed coating the walls of the flask. After one day of stirring at room temperature further potassium ferricyanide (330 mg, 1 mmol) and potassium hydroxide (168 mg, 3 mmol) dissolved in water (10 mL) were added and the mixture stirred for a further two days. The solution was filtered and then extracted with dichloromethane (3 x 10 mL). The reaction vessel was also rinsed

with dichloromethane (10 mL). The solvent was dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only nicotine.

Attempted synthesis of 42

40 (174 mg, 0.5 mmol) was dissolved in water (4 mL). Potassium ferricyanide (330 mg, 1 mmol) and potassium hydroxide (168 mg, 3 mmol) dissolved in water (10mL) were added over 30 minutes under argon, keeping the temperature under 15 °C. Ethanol (2 mL) was added to help dissolve the starting material, which was observed coating the walls of the flask. After one day of stirring at room temperature further potassium ferricyanide (330 mg, 1 mmol) and potassium hydroxide (168 mg, 3 mmol) dissolved in water (10 mL) were added and the mixture stirred for a further two days. The solution was filtered and then extracted with dichloromethane (3 x 10 mL). The reaction vessel was also rinsed with dichloromethane (10 mL). The solvent was dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only nicotine.

Attempted demethylation of nicotine to nornicotine by reaction with boron tribromide

Nicotine (324 mg, 2 mmol) was stirred with boron tribromide (5 mL) overnight at room temperature. The solution was carefully added to water (25 mL) and the solution neutralized with solid sodium carbonate. The solution was then extracted with dichloromethane (3 x 15 mL). The combine organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only nicotine.

Attempted demethylation of nicotine to nornicotine by reaction with refluxing trifluoroacetic acid

Nicotine (324 mg, 2 mmol) was stirred with trifluoroacetic acid (5 mL) overnight at room temperature. The solution was carefully added to water (25 mL) and the solution neutralized with solid sodium carbonate. The solution was then extracted with dichloromethane (3 x 15 mL). The combine organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only nicotine.

Attempted demethylation of nicotine to nornicotine using Pd/C in acetic acid

Nicotine (324 mg, 2 mmol) and palladium on carbon (20 mg) were placed in a dry flask with a magnetic flea. The flask was evacuated and flushed with argon gas carefully several times. After the final evacuation acetic acid (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After washing the plug with dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only nicotine.

Attempted debenzylation of 34 using Pearlman's Catalyst in acetic acid

Nicotine (324 mg, 2 mmol) and Pearlman's Catalyst (20 mg) were placed in a dry flask with a magnetic flea. The flask was evacuated and flushed with argon gas carefully several times. After the final evacuation acetic acid (5 mL) was added, and the solution was then exposed to a hydrogen atmosphere. The solution was stirred under a hydrogen atmosphere overnight, then filtered through a Celite plug to remove the catalyst. After washing the plug with dichloromethane the filtrate was reduced *in vacuo*. Analysis of the residue by ^{1}H-NMR revealed only nicotine.

2- and 6-aminonicotine

2- And 6-aminonicotine were synthesized by the method of Chichibabin.[45]

43

Nicotine (100 mg, 0.62 mmol) was dissolved in acetone (10 mL) and benzyl bromide (210 mg, 1.24 mmol) was added. The solution was stirred overnight at 50 °C, then cooled to room temperature. A pale yellow solid precipitated upon cooling, and was removed by filtration. The solid was washed with petroleum ether (5 mL) then diethyl ether (5 mL). Yield 50 mg (24 %). Spectroscopic data for the product matched literature values.[64]

Reaction of nicotine with 1,4-bisbromomethylbenzene

Nicotine (324 mg, 2 mmol) was added to a solution of 1,4-bis(bromomethyl)benzene (264 mg, 1 mmol) in acetone (20 mL). The solution was refluxed overnight. The solution was cooled and the solvent removed *in vacuo* to provide a brown tar. Analysis by ^{1}H-NMR revealed multiple products indicating substitution at both nitrogens of the nicotine molecule.

Reaction of nicotine with 1,3-bisbromomethylbenzene

Nicotine (324 mg, 2 mmol) was added to a solution of 1,3-(bisbromomethyl)benzene (264 mg, 1 mmol) in acetone (20 mL). The solution was refluxed overnight. The solution was cooled and the solvent removed *in vacuo* to provide a brown tar. Analysis by ^{1}H-NMR revealed multiple products indicating substitution at both nitrogens of the nicotine molecule.

Reaction of nicotine with 1,2-bisbromomethylbenzene

Nicotine (324 mg, 2 mmol) was added to a solution of 1,2-bis(bromomethyl)benzene (264 mg, 1 mmol) in acetone (20 mL). The solution was refluxed overnight. The solution was cooled and the solvent removed *in vacuo* to provide a brown tar. Analysis by ^{1}H-NMR revealed multiple products indicating substitution at both nitrogens of the nicotine molecule.

Reaction of nicotine with picolyl chloride hydrochloride in acetone

Nicotine (324 mg, 2 mmol) was added to a solution of picolyl chloride hydrochloride (328 mg, 2 mmol) in acetone (20 mL). The solution was refluxed overnight. The solution was cooled and the solvent removed *in vacuo* to provide a brown tar. Analysis by ^{1}H-NMR revealed multiple products indicating substitution at both nitrogens of the nicotine molecule.

45

Nicotine (200 mg, 1.24 mmol) and picolyl chloride hydrochloride (202 mg, 1.24 mmol) were dissolved in acetic acid (10 mL) and stirred overnight at room temperature. The solvent was removed *in vacuo* and water (20 mL) was added. The resulting solution was neutralized with solid sodium bicarbonate then extracted with dichloromethane (3 x 20 mL). The combined organic phases were

dried (Na_2SO_4) and the solvent removed *in vacuo* to provide the desired product as a brown oil. Yield 337 mg (94 %).

46

45 (337 mg, 1.17 mmol) was dissolved in water (5 mL) and added to a solution of potassium ferricyanide (900 mg) and potassium hydroxide (500 mg) in water (10 mL). The solution was stirred overnight under argon, then extracted with chloroform (3 x 20 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide the desired product as a pale brown oil. Yield 179 mg (57 %).

48

The synthesis of **48** was based on the synthesis of **47** by Woodward, Wendler and Brutschy.[65] Cinchonidine (2.94 g, 10 mmol) and benzophenone (9.1g, 50 mmol) were dissolved in absolute toluene (50 mL) and potassium *t*-butoxide (2.8 g, 25 mmol) was added. The solution was refluxed overnight under nitrogen, and then cooled to room temperature. The solution was poured onto ice (25 mL) and extracted with 10% hydrochloric acid (5 x 30 mL). The combined acid extracts were washed with diethyl ether (2 x 50 mL) and then added dropwise to an excess of ammonium hydroxide-ice. The off-white solid that precipitated was removed by extraction with diethyl ether (2 x 50mL). The combined diethyl ether extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide the desired product as an off-white solid. Yield 2.22 g (76 %). Slow evaporation of petroleum ether solution of the product provided crystals suitable for X-ray crystallography. NMR was consistent with two products (twice the number of expected peaks) and was not assigned.

55

Cinchonidine (100 mg, 0.34 mmol), triphenylphosphine (178 mg, 0.68 mmol) and carbon tetrabromide (124 mg, 0.37 mmol) were dissolved in toluene (10 mL), and the solution was stirred overnight at room temperature. The solution was extracted with dilute hydrochloric acid (2 M, 3 x 10 mL). The aqueous phase was

neutralized with saturated sodium bicarbonate solution and extracted with chloroform (3 x 15 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed *in vacuo* to provide **3.39** as a white solid. Yield 47 mg (47 %). M.p. 188-192 °C.

56

9-Amino-(9-deoxy)*epi*-quinine (**56**) was synthesized by literature methods.[67] The yield of the reaction was increased from an approximately 1:1 ratio of product:starting material, to a 10:1 ratio, by increasing the amount of hydrazoic acid solution from 12 mL to 40 mL, and by the use of dry glassware and anhydrous solvents. Unfortunately the original paper gave no details on the chromatographic conditions used to purify the product, and although extensive work was done in this area, purification was not achieved. It is postulated that the product is unstable to column chromatography.

Reaction of bis(benzonitrile)palladium chloride with 56

Bis(benzonitrile)palladium chloride (38 mg, 0.1 mmol) in chloroform (1.5 mL) was added to crude **56** (32 mg, 0.1 mmol) in dichloromethane, with a fine yellow precipitate forming immediately. The solution was reduced *in vacuo* and water (3 mL) was added. The precipitate was then filtered off as a yellow solid. Crude yield 38 mg. M.p. >330 °C. The solid was soluble only in DMF and DMSO. ^{1}H-NMR in d_6-DMSO indicated the presence of a product in which the palladium had coordinated, as well as some starting material. Attempted recrystallisation by slow diffusion of various solvents into a DMF solution of the product failed to produce any solid material.

58

Compound **57** (100 mg, 0.31 mmol) and pyridine-2-carboxaldehyde (40 mg, 0.37 mmol, 1.2 equivalents) were stirred in ethanol (10 mL) overnight. The solvent was removed *in vacuo* to provide a brown oil. ^{1}H-NMR confirmed the presence of the desired product, as well as pyridine-2-carboxaldehyde and quinine. All attempts at purification of the product failed.

Attempted synthesis of 59

Quinine (324 mg, 1 mmol) was stirred in anhydrous tetrahydrofuran under argon. Triethylamine (0.3 mL) and methanesulphonic acid (0.1 mL) were added and the solution was stirred overnight art room temperature. A product formed as a white solid which was removed by filtration and air dried. Analysis of the white solid by ^{1}H-NMR revealed only the starting material.

60

Cinchonidine (294 mg, 1 mmol) was stirred in anhydrous tetrahydrofuran under argon. Triethylamine (0.3 mL) and methanesulphonic acid (0.1 mL) were added and the solution was stirred overnight at room temperature. A white solid formed, and was removed by filtration. The white solid was dissolved in dichloromethane (10 mL) and extracted with water (2 x 10 mL). The organic phase was dried (Na_2SO_4) and reduced *in vacuo*, to provide the desired product as a white solid. Yield 357 mg (97 %).

Attempted synthesis of 62

60 (195 mg, 0.5 mmol) and sodium azide (162 mg, 2.5 mmol) in absolute DMF (4 mL) were stirred overnight at 80 °C under argon. A saturated aqueous solution of sodium bicarbonate (5 mL) was added and the resulting solution was extracted with dichloromethane (3 x 10 mL). The combined organic phases were reduced *in vacuo* and 1:1:1 water:diethyl ether:chloroform mixture (20 mL) was added. The solution was shaken well and separated. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*. Analysis by ^{1}H-NMR and ES-MS revealed only cinchonidine.

7.4 Chapter 4 Experimental

63

63 was synthesized by the method of Hartshorn[70]. Spectroscopic data for the product matched literature values.[70]

64

64 was synthesized by the method of Hartshorn[70]. Spectroscopic data for the product matched literature values.[89]

65

A solution of (*2S*)-proline (230 mg, 2 mmol) and sodium hydroxide (320 mg, 8 mmol) in water (5 mL) was added dropwise to a solution of picolyl chloride hydrochloride (361 mg, 2.2 mmol) in water (5 mL) and heated to reflux with stirring overnight. The solution was cooled, extracted with petroleum ether (2 x 20 mL), and then acidified to pH 4-5 with concentrated hydrochloric acid. The solvent was removed *in vacuo* and the residue stirred overnight in refluxing chloroform. The solution was cooled, dried (Na_2SO_4), solids removed by filtration, and the solvent removed *in vacuo* to give the product as a brown oil. Yield 395 mg (96 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.58 (1H, d, H6'), 7.69 (1H, dt, H4'), 7.36 (1H, d, H3'), 7.25-7.27 (1H, m, H5'), 4.21 (2H, dd, NCH_2py), 3.79 (1H, t, H2a), 3.46 (1H, p, H5b), 2.85 (1H, dd, H5a), 2.27 (2H, m, H3a, H3b), 1.92 (2H, m, H4a, H4b). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.80 (COOH), 154.68 (C2'), 149.42 (C6'), 137.26 (C4'), 123.55 (C3'), 123.32 (C5'), 67.89 (C2), 59.44 (NCH_2py), 54.39 (C5), 29.69 (C3), 24.21 (C4). ES-MS: Found M^+ 207.1136, $C_{11}H_{14}N_2O_2$ requires M^+ 207.1133. IR: 3387, 2991, 1632, 1595, 1441, 1393, 1315, 1053, 999, 772 cm^{-1}.

66

A solution of (*2S*)-proline (230 mg, 2 mmol) and sodium hydroxide (320 mg, 8 mmol) in water (5 mL) was added dropwise to a solution of nicotinyl chloride hydrochloride (361 mg, 2.2 mmol) in water (5 mL) and heated to reflux with

stirring overnight. The solution was cooled, extracted with petroleum ether (2 x 20 mL), and then acidified to pH 4-5 with concentrated hydrochloric acid. The solvent was removed *in vacuo* and the residue stirred overnight in refluxing chloroform. The solution was cooled, dried (Na_2SO_4), solids removed by filtration, and the solvent removed *in vacuo* to give the product as a brown oil.

67

A solution of (*2S*)-proline (230 mg, 2 mmol) and sodium hydroxide (320 mg, 8 mmol) in water (5 mL) was added dropwise to a solution of 4-chloromethylpyridine hydrochloride (361 mg, 2.2 mmol) in water (5 mL) and heated to reflux with stirring overnight. The solution was cooled, extracted with petroleum ether (2 x 20 mL), and then acidified to pH 4-5 with concentrated hydrochloric acid. The solvent was removed *in vacuo* and the residue stirred overnight in refluxing chloroform. The solution was cooled, dried (Na_2SO_4), solids removed by filtration, and the solvent removed *in vacuo* to give the product as a brown oil.

69

(*2S*)-(-)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (177 mg, 1 mmol), 2-chloromethylpyridine hydrochloride (180 mg, 1.1 mmol) and sodium hydroxide (0.3 g) were dissolved in water (5 mL). The solution was stirred and heated to reflux overnight. After cooling the solution was adjusted to pH ~7 and the solution left to stand for 30 minutes. The solution was filtered to remove the unreacted acid and the filtrate reduced *in vacuo*. The solid was stirred with dichloromethane (50 mL), then the organic phase was dried (Na_2SO_4) and reduced *in vacuo* to provide a sticky brown oil. This oil was dissolved in water (25 mL) and extracted with petroleum ether (4 x 40 mL) and then extracted with dichloromethane (3 x 30 mL). The combined dichloromethane fractions were dried (Na_2SO_4) and reduced in vacuo to provide the desired product as a sticky brown oil. Yield 160 mg (60 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.60 (1H, d, H6'), 7.75 (1H, dt, H4'), 7.44 (1H, d, H3'), 7.30 (1H, dd, H5'), 7.20-7.21 (2H, m, H5, H8), 7.04 & 7.15-7.18 (2H, m, H5, H8), 4.23 (1H, d, NCH_2a), 4.10 (1H, d, H10a), 4.08 (1H, d, NCH_2a), 3.88 (1H, d, H10b), 3.84 (1H, t, H2), 3.22-3.30 (2H, m, H3a, H3b). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.0 (COOH), 156.2 (C2'), 148.3 (C6'),

138.0 (C4'), 133.3 (C4), 132.9 (C9), 128.5 (C5), 127.3 (C8), 126.4 & 126.5 (C6, C7), 123.9 (C3'), 123.3 (C5'), 61.2 (C2), 59,5 (NCH_2), 51.7 (C10), 29.7 (C3). ES-MS: Found M^+ 269.1188, $C_{16}H_{16}N_2O_2$ requires M^+ 269.1290. IR: 3395, 3013, 2509, 1720, 1630, 1593, 1439, 1377, 1200, 766 cm^{-1}.

72

Picolinic acid (123 mg, 1 mmol) and toluene (2 mL) were placed in a dry round-bottomed flask, equipped with stir bar, under argon. The solution was stirred and sufficient triethylamine (~0.5 mL) was added dropwise to dissolve the solid. In some cases a sticky residue formed on the walls of the flask. The solution was cooled to 0 °C and ethyl chlorocarbonate (0.1 mL, ~1.1 mmol) was added dropwise. This addition was done with the syringe needle almost in the solution to reduce the reaction between ethyl chlorocarbonate and gaseous triethylamine. The solution was stirred for 15 minutes following completed addition. Alanine methyl ester hydrochloride (140 mg, 1 mmol) was dissolved in dry chloroform (5 mL) by the dropwise addition of triethylamine (~0.14 mL, ~1 mmol). The resulting solution was added dropwise to the cooled (0 °C) toluene solution. Following addition the solution was allowed to come to room temperature, and then stirred overnight. The solution was then extracted with water (15 mL), 3% sodium bicarbonate solution (20 mL) and again with water (15 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*, to provide the product as a pale brown oil. Yield 193 mg (93 %). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.59 (1H, d, H6'), 8.49 (1H, d, NH), 8.18 (1H, dd, H4'), 7.83-7.87 (1H, m, H3'), 7.43-7.46 (1H, m, H5'), 4.78-4.84 (1H, m, CH), 3.79 (3H, s, OMe), 1.54 (3H, d, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.08 (C1), 163.82 (CONH), 149.29 (C2'), 148.13 (C6'), 137.21 (C4'), 126.28 (C3'), 122.16 (C5'), 52.38 (OMe), 47.99 (C2), 18.32 (CH_3). IR: 3383, 2955, 1744, 1676, 1518, 1435, 1352, 1173, 752, 621 cm^{-1}.

70

72 (208 mg, 1 mmol) was dissolved in a 5 % lithium hydroxide solution in 3:1 methanol:water (10 mL). The solution was cooled to 5 °C overnight. The solution was extracted with dichloromethane (3 x 10 mL), the organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to provide the product as a white crystalline solid. Yield 190mg (98 %). Slow evaporation of a dichloromethane

solution provided crystals suitable for X-ray crystallography. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.59 (1H, d, H6'), 8.50 (1H, d, NH), 8.20 (1H, d, H3'), 7.87 (1H, t, H4'), 7.45-7.48 (1H, m, H5'), 4.81 (1H, p, CH), 1.62 (3H, d, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.26 (C1), 164.55 (CONH), 148.99 (C2'), 148.26 (C6'), 137.51 (C4'), 126.61 (C3'), 122.51 (C5'), 48.29 (C2), 17.95 (CH_3).

73

Picolinic acid (123 mg, 1 mmol) and toluene (2 mL) were placed in a dry round-bottomed flask, equipped with stir bar, under argon. The solution was stirred and sufficient triethylamine (~0.5 mL) was added dropwise to dissolve the solid. In some cases a sticky residue formed on the walls of the flask. The solution was cooled to 0 °C and ethyl chlorocarbonate (0.1 mL, ~1.1 mmol) is added dropwise. This addition was done with the syringe needle almost in the solution to reduce the reaction between ethyl chlorocarbonate and gaseous triethylamine. The solution was stirred for 15 minutes following completed addition. Valine methyl ester hydrochloride (168 mg, 1 mmol) was dissolved in dry chloroform (5 mL) by the dropwise addition of triethylamine (~0.14 mL, ~1 mmol). The resulting solution was added dropwise to the cooled (0 °C) toluene solution. Following addition the solution was allowed to come to room temperature, and then stirred overnight. The solution was then extracted with water (15 mL), 3% sodium bicarbonate solution (20 mL) and again with water (15 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*, to provide the product as a pale brown oil. Yield 201 mg (85 %). ^{1}H-NMR (500MHz, $CDCl_3$): 8.60 (1H, dd, H6'), 8.52 (1H, d, NH), 8.18 (1H, dd, H3'), 7.83-7.87 (1H, m, H4'), 7.43-7.46 (1H, m, H5'), 4.74 (1H, ddd, H3), 3.77 (3H, d, OMe), 2.30-2.36 (1H, m, H4), 1.01-1.04 (6H, m, H5).

74

73 (236 mg, 1 mmol) was dissolved in a 5 % lithium hydroxide solution in 3:1 methanol:water (10 mL). The solution was cooled to 5 °C overnight. The solution was extracted with dichloromethane (3 x 10 mL), the organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo* to provide the product as a white crystalline solid. Yield 203mg (91 %).

7.5 Chapter 5 Experimental

82

A solution of (2*R*,4*R*)-2-(2-pyridyl)-thiazolidine-4-carboxylic acid in 2:1 methanol:water (0.333 M, 6 mL) was added to a solution of hexa(aqua)cobalt(II) nitrate (29 mg, 0.1 mmol) in water (2 mL). Upon standing crystals suitable for X-ray crystallography were obtained. Yield 12 mg (20 %). M.p. 205-210 °C (dec.). Anal. Found: C, 37.02; H, 4.13; N, 11.92. Calc for $C_{18}H_{23}CoN_5O_{9.5}S_2$: C, 36.99; H, 3.97; N, 11.98. IR (KBr mull): 3526, 3017, 2937, 2864, 2401, 1651, 1558, 1479, 1385, 775 cm^{-1}.

83

A solution of (2*R*,4*R*)-2-(2-pyridyl)-thiazolidine-4-carboxylic acid in 2:1 methanol:water (0.333 M, 6 mL) was added to a solution of cobalt(II) bromide (22 mg, 0.1 mmol) in water (2 mL). Slow evaporation of the solvent resulted in crystals suitable for X-ray crystallography. Yield 13mg (23 %).

84

A solution of (2*R*,4*R*)-2-(2-pyridyl)-thiazolidine-4-carboxylic acid in 2:1 methanol:water (0.333 M, 6 mL) was added to a solution of hexa(aqua)nickel(II) nitrate (29 mg, 0.1 mmol) in water (2 mL). Upon standing crystals suitable for X-ray diffraction were obtained. Yield 30 mg (55 %). M.p. 223-226 °C (dec.). Anal. Found: C, 40.24; H, 3.65; N, 12.71. Calc for $C_{18}H_{19}N_5NiO_7S_2$: C, 40.02; H, 3.55; N, 12.96. IR (KBr mull): 3184, 3092, 2930, 1624, 1603, 1384, 1300, 1227, 916, 660, 419 cm^{-1}.

85

A solution of (2*R*,4*R*)-2-(2-pyridyl)-thiazolidine-4-carboxylic acid in 2:1 methanol:water (0.333 M, 6 mL) was added to a solution of nickel(II) sulphate heptahydrate (28.1 mg, 0.1 mmol) in water (2 mL). Upon standing crystals suitable for X-ray diffraction were obtained. Yield 25 mg (52 %). M.p. 229-232 °C (dec.). Anal. Found: C, 43.84; H, 4.09; N, 11.30. Calc for $C_{18}H_{20}N_4NiO_5S_2$:

C, 43.66; H, 4.07; N, 11.31. IR (KBr mull): 3130, 2986, 2930, 2766, 1597, 1570, 1477, 1443, 1387, 1350, 1294, 1151, 1088, 1056, 1024, 955, 843, 793 cm^{-1}.

86

A solution of (2*R*,4*R*)-2-(2-pyridyl)-thiazolidine-4-carboxylic acid in 2:1 methanol:water (0.333 M, 6 mL) was added to a solution of nickel(II) bromide trihydrate (27.2 mg, 0.1 mmol) in water (2 mL). Upon standing two different types of crystals formed, both of which were suitable for X-ray crystallography. The plate-like majority proved to have an identical unit cell to **85** and the structure was not pursued. A small rosette of crystals proved to have a different cell, and after several attempts a crystal suitable for X-ray crystallography was identified. Yield 8 mg (14 %). M.p. 220-230 °C (dec.). Anal. Found: C, 39.04; H, 3.50; N, 10.05. Calc for $C_{18}H_{19}BrN_4NiO_4S_2$: C, 38.74; H, 3.43; N, 10.04. IR (KBr mull): 3200 (br), 3101, 2885, 2361, 2341, 1626, 1607, 1479, 1429, 800 (br), 659 cm^{-1}.

87

A solution of (*S*)-N-(picolinamide)alanine methyl ester (21 mg, 0.1 mmol) in acetonitrile (1 mL) was added to a solution of copper(II) nitrate trihydrate (12 mg, 0.05 mmol) dissolved in acetonitrile (2 mL). The solution darkened immediately. Slow diffusion ofdiethyl ether into a 0.5 mL portion of this solution provided crystals suitable for X-ray diffraction. Yield 4 mg (80 %). M.p. 164-166 °C (dec.). Anal. Found: C, 39.81; H, 4.08; N, 13.75. Calc for $C_{20}H_{24}CuN_6O_{12}$: C, 39.77; H, 4.01; N, 13.91. IR (KBr mull): 3163, 2231, 1695, 1510, 1076, 977, 957, 870, 802, 733 cm^{-1}.

88

A solution of (*S*)-N-(picolinamide)alanine methyl ester (21 mg, 0.1 mmol) in acetonitrile (1 mL) was added to a solution of silver(I) perchlorate (11 mg, 0.05 mmol) dissolved in acetonitrile (2 mL). The solution was kept in the dark. Slow diffusion of ethyl acetate into a 0.5 mL portion, followed by almost complete evaporation of the solvent resulted in crystals suitable for X-ray crystallography. Yield >2 mg. M.p. undetermined. Anal. undetermined.

89

A solution of (*S*)-N-(picolyl)proline (21 mg, 0.1 mmol) in methanol (1 mL) was added to a solution of cobalt(II) bromide (11 mg, 0.05 mmol) in methanol (2 mL). Slow evaporation of the solvent result in crystals suitable for X-ray crystallography. Yield undetermined.

Appendices

Crystallography

Tables **A1**-**A5** list the crystal data and X-ray experimental details for the 22 crystal structures discussed in this thesis. Throughout the text, selected bond lengths and angles are discussed and listed under the appropriate figures, while the remaining distances and angles, as well as atomic coordinates, anisotropic displacement factors and hydrogen atom coordinates are available on request from the Department of Chemistry, University of Canterbury.

Two different diffractometers were used in the collection of crystal structures reported in this thesis, and different software packages were used for the data collection, cell determination and data reduction. Both detectors employed graphite monochromatized Mo Kα (λ = 0.71073 Å) radiation. The first diffractometer used was a Siemens CCD area detector mounted on a P4 four-circle diffractometer. Data collection and cell determination was performed with SMART[90] and data reduction with SAINT.[91] The second diffractometer used was an Bruker-Nonius APEX II system. Data collection, cell determination and data reduction were all performed with the APEX package of software.[92] All structures had intensities corrected for Lorentz and polarization effects and for absorption using SADABS.[93] All structures were solved by direct methods using SHELXS[94] and refined on F^2 using all data by full-matrix least-squares procedures using SHELXL-97.[95] All non-hydrogen atoms were refined with anisotropic displacement parameters where possible. Aromatic and non-terminal aliphatic hydrogen atoms were included in calculated positions with isotropic displacement factors 1.2 times the isotropic equivalent of their carrier atoms. Methyl protons were placed in calculated positions and allowed to rotate around the C-C axis, with isotropic displacement factors 1.5 times the isotropic equivalent of their carrier carbon atoms. Hydrogen atoms bonded to water molecules were located from the electron density map where possible and the O-H distance was restrained to 0.84 Å, with isotropic displacement factors 1.5 times the isotropic equivalent of their carrier oxygen atoms.

Table A1: Crystal data and X-ray experimental data for structures **1**, **2**, **3**, **4** and **6**.

Compound	**1**	**2**	**3**	**4**	**6**
Empirical Formula	$C_{24}H_{30}CoN_8S_4$	$C_{24}H_{30}NiN_8S_4$	$C_{24}H_{30}CuN_8S_4$	$C_{24}H_{30}CdN_8S_4$	$C_{24}H_{30}MnN_8S_4$
Formula Weight	617.73	617.51	622.34	671.20	613.74
Temperature (K)	168(2)	168(2)	168(2)	168(2)	168(2)
Crystal System	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space Group	C2	C2	$P2_1$	C2	C2
Unit cell dimensions: a (Å)	19.059(9)	18.94(2)	7.478(2)	19.505(4)	18.514(7)
b (Å)	10.772(5)	10.805(13)	10.850(4)	10.818(2)	10.606(4)
c (Å)	7.434(3)	7.435(9)	18.236(6)	7.4438(16)	7.321(3)
α (°)	90	90	90	90	90
β (°)	107.09(3)	106.88(4)	97.757(4)	106.141(2)	93.943(3)
γ (°)	90	90	90	90	90
Volume ($Å^3$)	1458.9(11)	1456(3)	1466.0(8)	1508.8(5)	1434.2(9)
Z	2	2	2	2	2
Density (calculated) (Mg/m^3)	1.406	1.409	1.410	1.477	1.421
Absorption coefficient (mm^{-1})	0.903	0.982	1.059	1.029	0.781
F(000)	642	644	646	684	638
Crystal size (mm^3)	0.50x0.50x0.35	0.50x0.50x0.50	0.44x0.31x0.26	0.50x0.50x0.20	0.50x0.50x0.50
Theta range for data collection (°)	2.19 to 26.37	2.19 to 26.40	2.25 to 26.35	2.17 to 26.26	2.21 to 26.47
Reflections collected	9430	26926	17924	9530	9042
Independent reflections [R_{int}]	2969 [0.0148]	2800 [0.0189]	5838 [0.0393]	2894 [0.0211]	2612 [0.2079]
Observed Reflections (for I>2σI)	2924	2750	5355	2890	2430
Data / restraints / parameters	2629 / 1 / 189	2800 / 1 / 189	5838 / 1 / 346	2894 / 1 / 169	2612 / 114 / 188
Goodness-of-fit on F^2	1.079	1.048	1.084	1.044	1.056
R_1 (for I>2σI)	0.0263	0.0455	0.0400	0.0395	0.1139
wR_2 (all data)	0.0691	0.1177	0.1043	0.1048	0.2976
Detector	SMART/CCD	SMART/CCD	SMART/CCD	SMART/CCD	SMART/CCD

Table A2: Crystal data and X-ray experimental data for structures **8**, **9**, **10**, **7** and **14**.

Compound	**8**	**9**	**10**	**7**	**14**
Empirical Formula	$C_{10}H_{14}AgN_3O_3$	$C_{20}H_{28}AgN_5O_3$	$C_{14}H_{20}AgBF_4N_4$	$C_{42}H_{56}N_{10}NiOS_2$	$C_{25}H_{25}Cl_2CuN_5O_8$
Formula Weight	332.11	494.34	439.02	839.80	657.94
Temperature (K)	170(2)	168(2)	168(2)	168(2)	168(2)
Crystal System	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space Group	$P2_12_12_1$	$P2_1$	$P2_1$	$P2_1$	P1
Unit cell dimensions: a (Å)	9.925(2)	9.376(3)	7.602(4)	13.636(17)	8.626(4)
b (Å)	11.276(2)	11.393(3)	11.134(5)	18.11(2)	10.137(5)
c (Å)	11.284(2)	10.262(3)	11.034(5)	19.24(2)	16.484(8)
α (°)	90	90	90	90	87.313(6)
β (°)	90	94.509(4)	90.352(6)	106.96(5)	78.631(6)
γ (°)	90	90	90	90	85.403(7)
Volume ($Å^3$)	1262.8(4)	1092.9(6)	933.9(8)	4543(9)	1407.9(11)
Z	4	2	2	4	2
Density (calculated) (Mg/m^3)	1.747	1.502	1.561	1.228	1.552
Absorption coefficient (mm^{-1})	1.597	0.952	1.119	0.562	1.022
F(000)	664	508	440	1784	674
Crystal size (mm^3)	0.50x0.35x0.30	0.42x0.21x0.13	0.50x0.40x0.20	0.40x0.35x0.15	0.12x0.11x0.04
Theta range for data collection (°)	2.55 to 26.00	1.99 to 26.38	2.60 to 26.28	1.92 to 26.41	2.02 to 26.44
Reflections collected	15118	13775	11193	58308	18001
Independent reflections [R_{int}]	2475 [0.0199]	4388 [0.0299]	3652 [0.0212]	18300 [0.0653]	9198 [0.0601]
Observed Reflections (for I>2σI)	2458	3998	3578	11489	5466
Data / restraints / parameters	2475 / 0 / 155	4388 / 1 / 264	3652 / 1 / 248	18300 / 822 / 1026	9198 / 602 / 741
Goodness-of-fit on F^2	1.101	0.979	1.064	1.020	0.969
R_1 (for I>2σI)	0.0160	0.0212	0.0297	0.0772	0.0701
wR_2 (all data)	0.0410	0.0466	0.0771	0.2356	0.1742
Detector	SMART/CCD	SMART/CCD	SMART/CCD	SMART/CCD	SMART/CCD

Table A3: Crystal data and X-ray experimental data for structures **15**, **17**, **48**, **70**, **82**.

Compound	**15**	**17**	**48**	**70**	**82**
Empirical Formula	$C_{44}H_{46}Cl_2Cu_2N_6O_4$	$C_{20}H_{24}Cl_2CoN_2O_2$	$C_{19}H_{20}N_2O$	$C_9H_{10}N_2O_3$	$C_{18}H_{24}CoN_5O_{10}S_2$
Formula Weight	464.46	454.24	292.37	194.19	593.47
Temperature (K)	168(2)	168(2)	93(2)	93(2)	93(2)
Crystal System	Monoclinic	Tetragonal	Monoclinic	Orthorhombic	Monoclinic
Space Group	$P2_1$	$P4_1$	C2	$P2_12_12_1$	$P2_1$
Unit cell dimensions: a (Å)	10.490(4)	9.336(14)	18.3643(16)	4.9239(10)	9.9472(5)
b (Å)	15.167(6)	9.336(14)	8.4333(7)	10.107(2)	10.2266(5)
c (Å)	13.510(5)	53.35(16)	20.4958(18)	18.813(4)	11.2600(6)
α (°)	90	90	90	90	90
β (°)	99.477(5)	90	102.400(2)	90	94.055(2)
γ (°)	90	90	90	90	90
Volume ($Å^3$)	2120.1(14)	4650(17)	3100.2(5)	936.2(3)	1142.57(10)
Z	2	8	8	4	2
Density (calculated) (Mg/m^3)	1.455	1.460	1.253	1.378	1.725
Absorption coefficient (mm^{-1})	1.179	1.106	0.078	0.105	1.001
F(000)	968	2115	1248	408	612
Crystal size (mm^3)	0.44x0.38x0.35	0.28x0.21x0.01	0.64x0.35x0.10	0.41x0.40x0.09	0.49x0.46x0.19
Theta range for data collection (°)	1.97 to 26.34	2.18 to 26.79	2.03 to 26.37	2.17 to 26.43	1.81 to 28.32
Reflections collected	26477	59759	13451	19635	28798
Independent reflections [R_{int}]	8302 [0.0505]	9741 [0.8181]	3340 [0.0341]	1155 [0.0246]	5649 [0.0254]
Observed Reflections (for I>2σI)	7327	1242	2721	1115	5641
Data / restraints / parameters	8302 / 1 / 527	9741 / 3 / 534	3340 / 1 / 397	1155 / 0 / 128	5649 / 10 / 343
Goodness-of-fit on F^2	1.122	0.525	0.976	1.061	1.034
R_1 (for I>2σI)	0.0456	0.0723	0.0364	0.0249	0.0245
wR_2 (all data)	0.0980	0.2362	0.0816	0.0671	0.0646
Detector	SMART/CCD	SMART/CCD	SMART/CCD	SMART/CCD	SMART/CCD

Table A4: Crystal data and X-ray experimental data for structures **83**, **84**, **85**, **86** and **87**.

Compound	**83**	**84**	**85**	**86**	**87**
Empirical Formula	$C_{18}H_{18}BrCoN_4O_4S_2$	$C_{18}H_{19}N_5NiO_7S_2$	$C_{18}H_{20}N_4NiO_5S_2$	$C_{18}H_{19}BrN_4NiO_4S_2$	$C_{20}H_{24}CuN_6O_{12}$
Formula Weight	557.32	540.21	495.21	558.11	603.99
Temperature (K)	93(2)	113(2)	113(2)	93(2)	93(2)
Crystal System	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space Group	$P2_12_12$	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_1$
Unit cell dimensions: a (Å)	9.7103(9)	10.4057(6)	7.1909(5)	10.569(3)	7.3304(3)
b (Å)	23.214(3)	8.7019(5)	8.3294(5)	8.467(3)	13.7677(8)
c (Å)	10.2377(9)	12.1900(7)	32.5916(19)	11.937(4)	12.2355(7)
α (°)	90	90	90	90	90
β (°)	90	105.916(1)	90	106.280(6)	92.301(2)
γ (°)	90	90	90	90	90
Volume ($Å^3$)	2307.7(4)	1061.48(11)	1952.1(2)	1025.3(5)	1233.84(11)
Z	4	2	4	2	2
Density (calculated) (Mg/m^3)	1.604	1.690	1.685	1.808	1.626
Absorption coefficient (mm^{-1})	2.687	1.164	1.249	3.133	0.962
F(000)	1120	556	1024	564	622
Crystal size (mm^3)	0.62x0.60x0.43	0.50x0.41x0.19	0.50x0.31x0.05	0.75x0.14x0.02	0.48x0.18x0.01
Theta range for data collection (°)	1.99 to 33.58	2.04 to 26.39	2.50 to 26.39	2.28 to 25.00	1.67 to 30.71
Reflections collected	28069	9232	17156	6170	21558
Independent reflections [R_{int}]	8486 [0.0518]	4309 [0.0183]	3965 [0.0326]	3059 [0.0413]	6454 [0.0470]
Observed Reflections (for I>2σI)	8120	4199	3706	2215	4936
Data / restraints / parameters	8486 / 263 / 281	4309 / 1 / 318	3965 / 2 / 271	3059 / 33 / 277	6454 / 1 / 365
Goodness-of-fit on F^2	1.260	1.039	1.049	0.961	1.011
R_1 (for I>2σI)	0.1451	0.0262	0.0254	0.0530	0.0426
wR_2 (all data)	0.3543	0.0691	0.0623	0.1242	0.0889
Detector	APEX II	SMART/CCD	SMART/CCD	SMART/CCD	SMART/CCD

Table A5: Crystal data and X-ray experimental data for structures **88** and **89**.

Compound	**88**	**89**
Empirical Formula	$C_{20}H_{24}AgClN_4O_{10}$	$C_{22}H_{26}BrCoN_4O_{4.5}$
Formula Weight	623.75	557.31
Temperature (K)	93(2)	93(2)
Crystal System	Orthorhombic	Tetragonal
Space Group	$P2_12_12_1$	$P4_22_12$
Unit cell dimensions: a (Å)	8.3738(2)	14.8674(10)
b (Å)	14.8936(4)	14.8674(10)
c (Å)	19.9557(6)	12.9005(8)
α (°)	90	90
β (°)	90	90
γ (°)	90	90
Volume ($Å^3$)	2488.80(12)	2847.1(3)
Z	4	8
Density (calculated) (Mg/m^3)	1.665	1.300
Absorption coefficient (mm^{-1})	0.978	2.038
F(000)	1264	1136
Crystal size (mm^3)	0.40x0.23x0.17	0.44x0.09x0.05
Theta range for data collection (°)	2.46 to 26.35	1.58 to 26.37
Reflections collected	28515	41976
Independent reflections [R_{int}]	5067 [0.0293]	3261 [0.1091]
Observed Reflections (for I>2σI)	4935	2610
Data / restraints / parameters	5067 / 0 / 329	3261 / 242 / 301
Goodness-of-fit on F^2	1.045	1.555
R_1 (for I>2σI)	0.0167	0.1292
wR_2 (all data)	0.0418	0.3661
Detector	APEX II	APEX II

References

References

[1] G. Wilkinson, R. D. Gillard and J. A. McCleverty, 'Comprehensive Coordination Chemistry : the Synthesis, Reactions, Properties and Applications of Coordination Compounds', Pergamon Press, Oxford, 1987.

[2] P. J. Steel, *Coord. Chem. Rev.*, 1990, **106**, 227; C. Kaes, A. Katz and M. W. Hosseini, *Chem. Rev.*, 2000, **100**, 3553.

[3] E. L. Eliel, S. H. Wilen and L. N. Mander, 'Stereochemistry of Organic Compounds', Wiley, New York, 1994.

[4] N. C. Fletcher and F. R. Keene, *J. Chem. Soc., Dalton Trans.*, 1999, 683.

[5] D. Lotscher, S. Rupprecht, H. Stoeckli-Evans and A. von Zelewsky, *Tetrahedron: Asymmetry*, 2000, **11**, 4341.

[6] I. V. Komarov and A. Borner, *Angew. Chem., Int. Ed.*, 2001, **40**, 1197; G. Buono, O. Chiodi and M. Wills, *Synlett*, 1999, 377; S. E. Denmark and R. A. Stavenger, *Acc. Chem. Res.*, 2000, **33**, 432; G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336.

[7] F. Fache, E. Schulz, M. L. Tommasino and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159; H. L. Kwong and W. S. Lee, *Tetrahedron: Asymmetry*, 2000, **11**, 2299; G. Chelucci, A. Saba, D. Vignola and C. Solinas, *Tetrahedron*, 2001, **57**, 1099.

[8] C. M. Fitchett and P. J. Steel, *New J. Chem.*, 2000, **24**, 945.

[9] A. Pfaltz, *Synlett*, 1999, 835.

[10] T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297.

[11] E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 1968.

[12] J. W. Steed and J. L. Atwood, 'Supramolecular Chemistry: A Concise Introduction', John Wiley & Sons, Chichester, UK, 2000.

[13] J. M. Lehn, 'Supramolecular Chemistry: Concepts and Perspectives', VCH, Weinheim, Germany, 1995.

[14] J.-M. Lehn, *Proc. Natl. Acad. Sci. USA*, 2002, **99**, 4763; J.-M. Lehn, *Science*, 2002, **295**, 2400; J.-M. Lehn and P. Ball, *New J. Chem.*, 2000, 300.

[15] G. R. Desiraju, *Acc. Chem. Res.*, 2002, **35**, 565; G. R. Desiraju, *Acc. Chem. Res.*, 1996, **29**, 441.

[16] C. Janiak, *Dalton*, 2000, 3885.

[17] E. C. Constable, *Chem. Ind.*, 1994, 56.

[18] B. Olenyuk, A. Fechtenkotter and P. J. Stang, *J. Chem. Soc., Dalton Trans.*, 1998, 1707; S. Leininger, B. Olenyuk and P. J. Stang, *Chem. Rev.*, 2000, **100**, 853; P. J. Stang and B. Olenyuk, *Acc. Chem. Res.*, 1997, **30**, 502; D. W. Johnson and K. N. Raymond, *Supramol. Chem.*, 2001, **13**, 639; C. J. Jones, *Chem. Soc. Rev.*, 1998, **27**, 289.

[19] M. Albrecht, *Chem.-Eur. J.*, 2000, **6**, 3485; M. Albrecht, *Chem. Rev.*, 2001, **101**, 3457; C. Piguet, G. Bernardinelli and G. Hopfgartner, *Chem. Rev.*, 1997, **97**, 2005.

[20] M. J. Zaworotko, *Chem. Commun.*, 2001, 1; B. Moulton and M. J. Zaworotko, *Chem. Rev.*, 2001, **101**, 1629; S. R. Batten and R. Robson, *Angew. Chem., Int. Ed.*, 1998, **37**, 1461.

[21] A. N. Khlobystov, A. J. Blake, N. R. Champness, D. A. Lemenovskii, A. G. Majouga, N. V. Zyk and M. Schröder, *Coord. Chem. Rev.*, 2001, **222**, 155.

[22] O. R. Evans and W. Lin, *Acc. Chem. Res.*, 2002, **35**, 511; O. R. Evans and W. Lin, *Chem. Mater.*, 2001, **13**, 3009; O. R. Evans and W. Lin, *Chem. Mater.*, 2001, **13**, 2705; O. R. Evans and W. Lin, *Dalton*, 2000, 3949; W. Lin, L. Ma and O. R. Evans, *Chem. Commun.*, 2000, 2263; W. Lin, Z. Wang and L. Ma, *J. Am. Chem. Soc.*, 1999, **121**, 11249; A. Jouaiti, M. W. Hosseini and N. Kyritsakas, *Chem. Commun.*, 2002, 1898.

[23] C. R. Smith, *J. Am. Chem. Soc.*, 1949, **71**, 2844; C. R. Smith, *J. Am. Chem. Soc.*, 1953, **75**, 2010.

[24] C. H. Koo and H. S. Kim, *Taehan Hwahakhoe Chi*, 1965, **9**, 134; R. B. Barlow, J. A. K. Howard and O. Johnson, *Acta Cryst.*, 1986, **C42**, 853.

[25] M. R. Udupa and B. Krebs, *Inorg. Chim. Acta*, 1980, **40**, 161.

[26] H. M. Haendler, *Acta Cryst.*, 1990, **C46**, 2054.

[27] N. Peulecke, C. Lefeber, A. Ohff, W. Baumann, A. Tillack, R. Kempe, V. V. Burlakov and U. Rosenthal, *Chem. Ber.*, 1996, **129**, 959.

[28] J. Guan and R. D. Fischer, *Eur. J. Inorg. Chem.*, 2001, 2497.

[29] G. Meyer, A. Berners and I. Pantenburg, *Z. Anorg. Allg. Chem.*, 2006, **632**, 34.

[30] P. Pytel, B. J. Oleksyn and J. Sliwinski, *Enantiomer*, 2001, **6**, 201; A. Skorska, B. J. Oleksyn and J. Sliwinski, *Enantiomer*, 2002, **7**, 295; A. Skorska, K. Stadnicka and B. J. Oleksyn, *Chirality*, 2005, **17**, 73.

[31] R. Hubel, K. Polborn and W. Beck, *Eur. J. Inorg. Chem.*, 1999, 471.

[32] Y.-R. Xie, X.-S. Wang, H. Zhao, J. Zhang, L.-H. Weng, C.-Y. Duan, R.-G. Xiong, X.-Z. You and Z.-L. Xue, *Organometallics*, 2003, **22**, 4396.

[33] Z.-R. Qu, Z.-F. Chen, J. Zhang, R.-G. Xiong, B. F. Abrahams and Z.-L. Xue, *Organometallics*, 2003, **22**, 2814.

[34] C. Missling, S. Mihan, K. Polborn and W. Beck, *Chem. Ber.*, 1996, **129**, 331.

[35] J. F. Whidby and J. I. Seeman, *J. Org. Chem.*, 1976, **41**, 1585.

[36] T. P. Pitner, W. B. Edwards, III, R. L. Bassfield and J. F. Whidby, *J. Am. Chem. Soc.*, 1978, **100**, 246.

[37] J. I. Seeman, H. V. Secor, C. G. Chavdarian, E. B. Sanders, R. L. Bassfield and J. F. Whidby, *J. Org. Chem.*, 1981, **46**, 3040.

[38] B. J. O'Keefe and P. J. Steel, *Inorg. Chem. Commun.*, 2007, **10**, 247; C. M. Fitchett and P. J. Steel, *Dalton Trans.*, 2006, 4886; J. Burgess, J. R. A. Cottam and P. J. Steel, *Aust. J. Chem.*, 2006, **59**, 295; M. R. A. Al-Mandhary, C. M. Fitchett and P. J. Steel, *Aust. J. Chem.*, 2006, **59**, 307; J. R. A. Cottam and P. J. Steel, *J. Organomet. Chem.*, 2006, **691**, 2286; M. R. A. Al-Mandhary and P. J. Steel, *Eur. J. Inorg. Chem.*, 2004, 329; P. J. Steel and C. J. Sumby, *Dalton Trans.*, 2003, 4505; C. Richardson and P. J. Steel, *Eur. J. Inorg. Chem.*, 2003, 405; D. A. McMorran and P. J. Steel, *J. Chem. Soc., Dalton Trans.*, 2002, 3321; P. J. Steel and C. J. Sumby, *Inorg. Chem. Commun.*, 2002, **5**, 323; C. M. Fitchett and P. J. Steel, *Inorg. Chim. Acta*, 2000, **310**, 127; C. M. Hartshorn and P. J. Steel, *Inorg. Chem. Commun.*, 2000, **3**, 476.

[39] C. Richardson and P. J. Steel, *Aust. J. Chem.*, 2002, **55**, 783.
[40] W. Lewis and P. J. Steel, *Supramol. Chem.*, 2005, **17**, 579.
[41] J. W. Slater, D. M. D'Alessandro, F. R. Keene and P. J. Steel, *Dalton Trans.*, 2006, 1954; J. A. Zampese, F. R. Keene and P. J. Steel, *Dalton Trans.*, 2004, 4124; A. J. Downard, I. G. Phillips and P. J. Steel, *Aust. J. Chem.*, 2004, **57**, 865; D. M. D'Alessandro, F. R. Keene, P. J. Steel and C. J. Sumby, *Aust. J. Chem.*, 2003, **56**, 657; C. Richardson and P. J. Steel, *Dalton Trans.*, 2003, 992; C. Richardson, P. J. Steel, D. M. D'Alessandro, P. C. Junk and F. R. Keene, *J. Chem. Soc., Dalton Trans.*, 2002, 2775; C. Richardson and P. J. Steel, *Aust. J. Chem.*, 2000, **53**, 93; C. Richardson and P. J. Steel, *Inorg. Chem. Commun.*, 2000, **3**, 155; C. M. Hartshorn and P. J. Steel, *Organometallics*, 1998, **17**, 3487; I. G. Phillips and P. J. Steel, *Aust. J. Chem.*, 1998, **51**, 371; C. M. Hartshorn and P. J. Steel, *Angew. Chem., Int. Ed.*, 1996, **35**, 2655; I. G. Phillips and P. J. Steel, *Inorg. Chim. Acta*, 1996, **244**, 3; A. J. Downard, P. J. Steel and J. Steenwijk, *Aust. J. Chem.*, 1995, **48**, 1625; A. J. Downard, G. E. Honey and P. J. Steel, *Inorg. Chem.*, 1991, **30**, 3733; A. J. Downard, G. E. Honey, L. F. Phillips and P. J. Steel, *Inorg. Chem.*, 1991, **30**, 2259; A. A. Watson, D. A. House and P. J. Steel, *Inorg. Chim. Acta*, 1987, **130**, 167.
[42] J. M. Calvert, R. H. Schmehl, B. P. Sullivan, J. S. Facci, T. J. Meyer and R. W. Murray, *Inorg. Chem.*, 1983, **22**, 2151.
[43] K. M. Anderson, K. Afarinkia, H.-w. Yu, A. E. Goeta and J. W. Steed, *Cryst. Growth Des.*, 2006, **6**, 2109; G. R. Desiraju, *CrystEngComm*, 2007, **9**, 91.
[44] B. Schmidt and V. Neitemeier, *Synthesis*, 1998, 42.
[45] A. E. Chichibabin and A. V. Kirssanov, *Chem. Ber.*, 1924, **57B**, 1163.
[46] J. I. Seeman, C. G. Chavdarian, R. A. Kornfeld and J. D. Naworal, *Tetrahedron*, 1985, **41**, 595; J. I. Seeman, L. E. Clawson and H. V. Secor, *Synthesis*, 1985, 953.
[47] R. M. Acheson, M. J. Ferris and N. M. Sinclair, *J. Chem. Res., Synop.*, 1979, 333.
[48] N. D. P. Cosford, L. Bleicher, A. Herbaut, S. McCallum, J.-M. Vernier, H. Dawson, J. P. Whitten, P. Adams, L. Chavez-Noriega, L. D. Corea, J. H. Crona, K. A. Stauderman, K. Whelan, G. K. Lloyd and M. I. A., *J. Med. Chem.*, 1996, **39**, 3235.
[49] A. Johansson and T. Svensson, in 'Preparation of 6-Substituted (S)-Nicotine Derivatives and Intermediates in their Preparation', WO #0170730, 2001
[50] F. C. Fevrier, E. D. Smith and D. L. Comins, *Org. Lett.*, 2005, **7**, 5457.
[51] H. M. R. Hoffmann and J. Frackenpohl, *Eur. J. Org. Chem.*, 2004, 4293.
[52] M. I. Damaj, W. Glassco, M. Dukat, E. L. May, R. A. Glennon and B. R. Martin, *Drug Dev. Res.*, 1996, **38**, 177.
[53] J.-P. Roduit, A. Wellig and A. Kiener, *Heterocycles*, 1997, **45**, 1687.
[54] D. Rolf, D. J. W. Goon and R. H. Michelson, in 'Preparation of Cotinine by Reacting Nicotine with Bromide and Bromate', Us #5625070, 1997
[55] E. C. Taylor, Jr. and N. E. Boyer, *J. Org. Chem.*, 1959, **24**, 275.
[56] E. N. Shaw, in 'Pyridine *N*-Oxides', ed. E. Klingsberg, Interscience Publishers, Inc., New York, 1961.

[57] Y. Kato, S. Okada, K. Tomimoto and T. Mase, *Tetrahedron Lett.*, 2001, **42**, 4849.
[58] O. Sugimoto, M. Mori and K.-i. Tanji, *Tetrahedron Lett.*, 1999, **40**, 7477.
[59] D. A. McMorran and P. J. Steel, *Tetrahedron*, 2003, **59**, 3701.
[60] F.-X. Felpin, S. Girard, G. Vo-Thanh, R. J. Robins, J. Villieras and J. Lebreton, *J. Org. Chem.*, 2001, **66**, 6305; S. Deloisy, H. Tietgen and H. Kunz, *Collect. Czech. Chem. Commun.*, 2000, **65**, 816; T.-P. Loh, J.-R. Zhou, X.-R. Li and K.-Y. Sim, *Tetrahedron Lett.*, 1999, **40**, 7847; J. H. Swango, B. S. Bhatti, M. M. Qureshi and P. A. Crooks, *Chirality*, 1999, **11**, 316; N. J. Joyce and E. Leete, *Heterocycles*, 1989, **29**, 1335.
[61] J. I. Seeman, C. G. Chavdarian and H. V. Secor, *J. Org. Chem.*, 1985, **50**, 5419; P. Jacob, III, *J. Org. Chem.*, 1982, **47**, 4165.
[62] S. Yamada, T. Sakai and M. Ohashi, *Heterocycles*, 1987, **25**, 287.
[63] R. D. Sindelar, J. P. Rosazza and C. F. Barfknecht, *Appl. Environ. Microbiol.*, 1979, **38**, 836.
[64] K. Yoshizawa, Y. In, T. Ishida and T. Shioiri, *Heterocycles*, 2005, **66**, 667.
[65] R. B. Woodward, N. L. Wendler and F. J. Brutschy, *J. Am. Chem. Soc.*, 1945, **67**, 1425.
[66] W. M. Braje, J. Holzgrefe, R. Wartchow and H. M. R. Hoffmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 2085.
[67] H. Brunner, J. Buegler and B. Nuber, *Tetrahedron: Asymmetry*, 1995, **6**, 1699.
[68] O. Mitsunobu, M. Wada and T. Sano, *J. Am. Chem. Soc.*, 1972, **94**, 697.
[69] R. Nakon, P. R. Rechani and R. J. Angelici, *Inorg. Chem.*, 1973, **12**, 2431; X. Wang, J. D. Ranford and J. J. Vittal, *J. Mol. Struct.*, 2006, **796**, 28; D.-H. Lee, *J. Korean Chem. Soc.*, 2003, **47**, 427; H. Yasuda, T. Kawaguchi, H. Yamamura and M. Kawai, *Peptide Science*, 2003, **39th**, 413; K. Yamato, I. Miyahara, A. Ichimura, K. Hirotsu, Y. Kojima, H. Sakurai, D. Shiomi, K. Sato and T. Takui, *Chem. Lett.*, 1999, 295; L. A. Meiske and R. J. Angelici, *Inorg. Chem.*, 1980, **19**, 3783.
[70] R. M. Hartshorn and S. G. Telfer, *Dalton*, 2000, 2801.
[71] T. Moriuchi, M. Nishiyama, K. Yoshida and T. Hirao, *Heterocycles*, 2006, **67**, 375; M. Ruf, R. Burth, K. Weis and H. Vahrenkamp, *Chem. Ber.*, 1996, **129**, 1251.
[72] C. J. Sumby, 'The Synthesis and Study of Bridging Heterocyclic Ligands', Canterbury University, Christchurch, 2003.
[73] M. K. Levadala, S. R. Banerjee, K. P. Maresca, J. W. Babich and J. Zubieta, *Synthesis*, 2004, 1759.
[74] K. V. Reddy, S. J. Jin, P. K. Arora, D. S. Sfeir, S. C. F. Maloney, F. L. Urbach and L. M. Sayre, *J. Am. Chem. Soc.*, 1990, **112**, 2332.
[75] Z. Budesinsky, A. Emr, V. Musil, Z. Perina and E. Zikmund, *Cesk. Farm.*, 1960, **9**, 179.
[76] J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids. 3 Vols', John Wiley & Sons Inc., New York, 1961.
[77] R. Garcia-Rodriguez and D. Miguel, *Dalton Trans.*, 2006, 1218; R. S. Herrick, I. Wrona, N. McMicken, G. Jones, C. J. Ziegler and J. Shaw, *J. Organomet. Chem.*, 2004, **689**, 4848.
[78] J. Yao, Y. Wu, H. Li and B. He, *Yingyong Huaxue*, 1998, **15**, 89.
[79] H. Li, J. Yao and B. He, *Sci. China Ser. B*, 1997, **40**, 485.

[80] H. Li, J. Yao and B. He, *Cuihua Xuebao*, 1997, **18**, 341; R. Riemschneider and G. A. Hoyer, *Z. Naturforsch*, 1963, **18B**, 25.
[81] H. Brunner, R. Becker and G. Riepl, *Organometallics*, 1984, **3**, 1354.
[82] Z. Zhang, A. E. Martell, R. J. Motekaitis and L. Fu, *Tetrahedron Lett.*, 1999, **40**, 4615; Z. Gyorgydeak, L. Szilagyi, J. Kajtar, G. Argay and A. Kalman, *Montash. Chem.*, 1994, **125**, 189; T. Mase, H. Hara, H. Nagaoka, T. Suzuki, T. Takahashi, K. Tomioka and T. Yamada, in 'Preparation of Pyridylthiazolidine Derivatives as Platelet-Activating Factor (PAF) Antagonists', JP #02049726, 1990; V. M. Kulkarni and H. P. Tipnis, *Curr. Sci. India*, 1972, **41**, 637.
[83] A. H. Cook and I. M. Heilbron, in 'Thiazolidines', ed. H. T. Clarke, J. R. Johnson and R. Robinson, Princeton Univ. Press, Princeton, NJ, 1949.
[84] H. Brunner, D. Mijolovic and M. Zabel, *Synthesis*, 2001, 1671.
[85] T. Moriuchi, M. Nishiyama, K. Yoshida, T. Ishikawa and T. Hirao, *Org. Lett.*, 2001, **3**, 1459; W. Guo, J. He, Z. Li and J.-P. Cheng, *Tetrahedron Lett.*, 2004, **45**, 5763; V. Derdau, E. Laschat, E. Hupe, W. A. Hupe, I. Dix and P. G. Jones, *Eur. J. Inorg. Chem.*, 1999, 1001; D. Ranganathan, V. Haridas, R. Gilardi and I. L. Karle, *J.Am.Chem.Soc.*, 1998, **120**, 10793; H. Zhao and W. Hua, *J. Org. Chem.*, 2000, **65**, 2933.
[86] M. Otsuka, H. Satake, S. Murakami, M. Doi, T. Ishida, M. Shibasaki and Y. Sugiura, *Bioorg. Med. Chem.*, 1996, **4**, 1703; H. Kurosaki, R. K. Sharma, S. Aoki, T. Inoue, Y. Okamoto, Y. Sugiura, M. Doi, T. Ishida, M. Otsuka and M. Goto, *J. Chem. Soc., Dalton Trans.*, 2001, 441; A. C. Joussef, A. S. Ceccato, A. J. Bortoluzzi, M. A. de Brito and S. M. Drechsel, *Acta Cryst.*, 2001, **E57**, m224; X. Shen, T. Moriuchi and T. Hirao, *Tetrahedron Lett.*, 2004, **45**, 4733; T. Kato, K. Sugimoto and M. Yamasaki, *Acta Cryst.*, 2001, **C57**, 1256.
[87] S. Gosiewska, J. J. L. M. Cornelissen, M. Lutz, A. L. Spek, G. Van Koten and R. J. M. Klein Gebbink, *Inorg. Chem.*, 2006, **45**, 4214; T. Nagata, Y. Kikuzawa and A. Osuka, *Inorg. Chim. Acta*, 2003, **342**, 139; K. Bernauer, P. Schurmann, C. Nusbaumer, L. Verardo and S. Ghizdavu, *Pure Appl. Chem.*, 1998, **70**, 985; H. J. Hilgers and K. Bernauer, *Inorg. Chim. Acta*, 1998, **275-276**, 9; K. Bernauer, D. Hugi-Cleary, H. J. Hilgers, H. Abd-el-Khalek, N. Brugger and C. Kressl, *Inorg. Chim. Acta*, 1998, **275-276**, 1; K. Bernauer and M.-F. Gilet, *Chem. Commun.*, 1997, 1287; K. Bernauer, E. Fuchs and D. Hugi-Cleary, *Inorg. Chim. Acta*, 1994, **218**, 73; K. Bernauer, H. Stoeckli-Evans, D. Hugi-Cleary, H. J. Hilgers, H. Abd-el-Khalek, J. Porret and J. J. Sauvain, *Helv. Chim. Acta*, 1992, **75**, 2327; K. Bernauer, M. Monzione, P. Schuermann and V. Viette, *Helv. Chim. Acta*, 1990, **73**, 346; K. Bernauer, P. Pousaz, J. Porret and A. Jeanguenat, *Helv. Chim. Acta*, 1988, **71**, 1339.
[88] A. L. Spek, *J. Appl. Cryst.*, 2003, **36**, 7.
[89] Y. Yoshikawa, K. Kawabe, M. Tadokoro, Y. Suzuki, N. Yanagihara, A. Nakayama, H. Sakurai and Y. Kojima, *Bull. Chem. Soc. Japan*, 2002, **75**, 2423.
[90] Bruker-AXS, SMART V5.054, 1997-1998
[91] Bruker-AXS, SAINT+ V6.22, 1997-2001
[92] Bruker-Nonius, Apex V2.02, 2005-2006
[93] G. M. Sheldrick, SADABS V1.0, 1998
[94] G. M. Sheldrick, *Acta Cryst.*, 1990, **A46**, 467.

[95] G. M. Sheldrick, SHELX-97 1997